A Longitudinal Study to Identify IBS Phenotypes Using Fecal Microbiota and Hydrogen Breath Testing

NCT03219528

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UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: A Longitudinal Study to Identify IBS Phenotypes Using Fecal Microbiota and Hydrogen Breath Testing (HUM00129427)
Company or agency sponsoring the study: Michigan Institute for Clinical and Health Research
Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable): Principal Investigator: Allen Lee, MD, Department of Internal Medicine, University of Michigan
Study Coordinator:
Almo Regazi, Department of Internal Medicine, University of Michigan
Samantha Brehmer, Department of Internal Medicine, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research collects health-related information, stool samples, and hydrogen breath test results to better understand irritable bowel syndrome with diarrhea (IBS-D). Additionally, if you consent to the optional studies listed in Section 4, colon tissue biopsies, saliva samples, and blood samples may be collected to better understand IBS-D. This research will investigate if Rifaximin and/or low FODMAP diet (FODMAP is an acronym that stands for Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols. FODMAP are sugars (carbohydrates) in the foods we eat that are poorly absorbed by the gut) will improve symptoms observed in IBS-D patients. We want to see if we can better classify IBS patients based on the results of hydrogen breath tests or by the composition of stool bacteria. If you choose to participate, you will be asked to either take Rifaximin or be on a low FODMAP diet (randomized), fill out surveys, record food diaries, collect stool samples, take hydrogen breath tests, answer questions online, and come to research visits at the hospital, and attend phone visits over the course of about 5 weeks.

This study involves a process called randomization. This means that the treatment (Rifaximin or low FODMAP diet) you receive in the study is not chosen by you or the researcher. The study design divides study

participants into separate groups, based on chance (like the flip of a coin), to compare different treatments or procedures. If you decide to be in the study, you need to be comfortable not choosing which study group you will be in.

This study may require you to stop taking certain medications before and possibly during the research study. If you decide to be in the study, you should understand that some symptoms that were controlled by that medication may worsen.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, these risks may include abdominal pain, bloating, dizziness, faint spells, and flatulence related to the drink consumed during the hydrogen breath test. General antibiotics side effects such as nausea, vomiting, diarrhea, etc may occur for patients taking Rifaximin. There could be pain or bruising associated with the optional blood draws. There are rare concerns about private information. More detailed information will be provided later in this document.

This study may offer some benefit to you now or others in the future by providing new insight into the causes and treatments of symptoms in IBS patients. Participants with IBS-D will receive glucose hydrogen breath tests to determine if they have small intestinal bacterial overgrowth (SIBO). Furthermore, IBS-D participants will be treated with well accepted treatments for IBS, including a non-absorbable antibiotic rifaximin or diets low in FODMAP. IBS-D subjects treated with low FODMAP diet will be provided education on a low FODMAP diet from a trained bio nutritionist and stool samples compensation. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be approximately 5 weeks.

You can decide not to be in this study. Alternatives to joining this study may include treatments such as anti-spasmodic, anti-depressants, antibiotics, and dietary modification. However, any alternative treatment option should be undertaken with appropriate continued medical supervision.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
Treatments such as a non-absorbable antibiotic called rifaximin or a diet low in FODMAP may improve symptoms in patients with irritable bowel syndrome (IBS). We believe these treatments work by affecting the intestinal bacteria in our gut. However, this has never been proven. Also, we do not yet have a way to predict who will respond best to treatments in IBS, such as rifaximin or a low FODMAP diet. We want to see if we can better classify IBS patients based on the results of tests, such as a glucose hydrogen breath test or by the composition of stool bacteria. A hydrogen breath test is looking for a condition called small intestinal bacterial overgrowth (SIBO). We also want to see if treatments for IBS lead to changes in the stool microbiome or hydrogen breath test results.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?
All adult subjects over the age of 18 years with diarrhea-predominant irritable bowel syndrome (IBS-D) are eligible to participate in this study. You cannot have a history of celiac disease (allergy to wheat products), microscopic colitis, inflammatory bowel disease such as ulcerative colitis or Crohn's disease, or other causes that might explain your symptoms.

You should have had a colonoscopy or flexible sigmoidoscopy with colon biopsies within the past 2 years to rule out a condition called microscopic colitis.

You will undergo an online survey for approximately seven days. You will be asked to fill out multiple choice questions about your IBS symptoms, and the study team will evaluate your symptoms to determine study eligibility.

Subjects with a history of surgery to the GI tract, other than removal of the appendix, are not eligible to participate in this study. Women who are pregnant or breastfeeding will not be allowed to participate in this study. A urine pregnancy test will be performed in women capable of bearing children to exclude the possibility that you are pregnant. In addition, you will not be eligible to participate in this study if you have been on antibiotics within the previous 3 months, such as rifaximin, or received dietary advice, such as a low FODMAP diet, for treatment of IBS or SIBO in the past.

In addition, adult IBS-D subjects and healthy adults who are scheduled for a colonoscopy are eligible to participate in an optional portion of the study where we will collect biopsy samples during your colonoscopy to determine how the microbiome (gut microbes) interact with the lining of the gut.

3.2 How many people are expected to take part in this study?
225 subjects with IBS-D as well as 25 healthy subjects will participate in this study.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?
You will undergo the following:

Pre-Visit (all subjects):

- To determine eligibility, you will undergo an online survey for approximately seven days. You will be asked to fill out multiple choice questions about your IBS symptoms. You will be asked questions about your social and medical history by a study coordinator. Depending on your symptoms, you may then be asked to come in/phone or video visit to go over the details of the study.
- Consent could be obtained via email, fax, mail, or SignNow (a secure online application).
- If you will undergo a colonoscopy to investigate the cause of your symptoms and you agree to participate in the optional sub study #2, you will also be asked to sign the consent form for optional sub study #2. During the colonoscopy, we may collect up to 12 mucosal biopsies during your routine colonoscopy. Each biopsy sample is about 0.2 cm in size which is approximately the size of a sesame seed. You are free to decline participation if you do not want to participate in this sub-study.
- You will be given instructions and supplies for stool collection. The quantity of stool collections will vary based on your participation in other sub studies associated with this study. All subjects will collect a minimum of three stool samples and bring them to their next visit if you have an in-person visit or you can mail it back to us as soon as possible.
- Wash-out period: We will ask that you discontinue the following medications for at least 1 month prior to enrollment: narcotic pain medications (e.g. Norco, Percocet, Morphine); and probiotics. We will ask that you stop antibiotics for at least 3 months prior to enrollment.

(Healthy Participants and IBS-D Subjects Undergoing Colonoscopy):

- You will complete a one-time symptom questionnaire to look at the severity of your GI and psychological symptoms.

(IBS-D Participants):

- You will be randomized to either rifaximin or the low FODMAP diet arm of the study before your visit 1. You will be told what treatment you have been randomized to. There is a 50:50 chance you will be put into either group, like a coin flip.
- You will also learn how to complete the dietary recalls and fill them out over 3 days to determine your typical diet as well as an abdominal pain, bloating, and bowel movement log before your visit 1.
- We will also ask that you avoid Pepto-Bismol for at least 2 weeks, not eat or drink for at least 8 hours and not smoke for at least 6 hours prior to the Glucose Hydrogen Breath Test.
- Participants not required to attend visit one in person will receive a hydrogen breath test kit and rifaximin via mail.

Rifaximin Group:

Visit 1 (Phone or in person visit):

You will be asked to complete questionnaires that determine the severity of your GI symptoms and drop off/mail your stool samples, three-day food diary, and logs. We will also provide a glucose hydrogen breath test kit for you to perform at home for the duration of the pandemic. You will receive Rifaximin during visit one either in-person at the clinic or via mail if conducted remotely. Female participants capable of bearing children or consented to the optional sub study #2 and/or #3, will have visit one conducted in-person with an approximate duration of 30 minutes. Male participants and female participants not capable of bearing children who have not consented to optional sub study #2 and #3 will be able to conduct the visit remotely during the pandemic.

- Questionnaires – you will complete eight questionnaires to look at the severity of your GI and psychological symptoms.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements only if visit is conducted in person.
- Urine pregnancy test – Women capable of bearing children will undergo a urine pregnancy test.

- Please do not take Peptobismol for at least 2 weeks before the test. You also should fast for at least 8 hours and should not smoke for at least 6 hours before the test. These restrictions will help improve the accuracy of the test.
- There should be another person available in case there a side effects of dizziness or lightheadedness. There should also be snacks readily available.
- Glucose Hydrogen Breath Test – you will be asked to drink a sugar water drink. You will then be asked to blow into a tube every 15 minutes for 2 hours to measure whether you have overgrowth of bacteria in your small intestine. The hydrogen breath test will be done remotely with a take home test kit.
- After you complete the glucose hydrogen breath test, you will then start on an antibiotic called rifaximin. You will take this medication three times per day for a total of 14 days.
- Should you choose to participate in the optional sub-study #2, you will provide a saliva sample, which will be self-collected in a provided kit. The sample size will be about 2mL, or approximately ½ teaspoon. These samples will be stored for genetic analysis related to enzymes pertaining to IBS-D and may be shared with investigators at other institutions (Karolinska Institute and IKMB Kiel) to run specialized tests. You are free to decline participation if you do not want to have your saliva sample stored. You will have the ability to accept or decline separate permission at the end of this consent document.
- Should you choose to participate in the optional sub-study #3, you will have your blood drawn. A trained phlebotomist will collect 1 tube, a total of about 10mL or 2 teaspoons of blood. These blood samples will be stored for future IBS-D research. You are free to decline participation if you do not want to have your blood sample stored. You will have the ability to accept or decline separate permission at the end of this consent document.
- You will be asked to record your stool frequency and form each day online or on paper log.
- You will also record the severity of your abdominal pain and bloating each day online or on paper log.
- You will also record your diet over a 24-hour period every week.

Visit 2 (Phone or In-Person Visit - Approximately one week after Visit 1):

- You will be asked questions about your medication compliance.
- You will continue to record your stool frequency and form, abdominal pain, and bloating online or on paper.
- You will have completed your 24-hour food recall by this time.
- You will be asked if you have experienced any adverse medical events since you last met the study team.
- You will be asked questions about your physical health and wellbeing.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements if the visit is conducted in person.

Visit 3 (Phone or In-Person Visit - Approximately one week after Visit 2):

- You will collect a stool sample before your third visit. You can return it to us in-person if you have an in-person visit or you will mail it to us as soon as possible.
- Questionnaires – you will complete eight questionnaires to look at the severity of your GI and psychological symptoms.
- You will be asked questions about your medication compliance. If you have been taking the medication as instructed, you should be finished with your rifaximin at this point.
- You will continue to record your stool frequency and form, abdominal pain, and bloating online or on paper.

- You will have completed your 24-hour food recall by this time.
- You will be asked if you have experienced any adverse medical events since you last met the study team
- You will be asked questions about your physical health and wellbeing.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements if the visit is conducted in person.

Visit 4 (Phone or In-Person Visit - Approximately two weeks after Visit 3)**:**

- You will collect a stool sample before your fourth visit. You can return it to us in-person if you have an in-person visit or you will mail it to us as soon as possible.
- You will have completed your 24-hour food recall by this time.
- You will continue to record your stool frequency and form, abdominal pain, and bloating online.
- You will be asked if you have experienced any adverse medical events since you last met with the study team.
- You will be asked questions about your physical health and wellbeing.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse and temperature measurements if the visit is conducted in person.

Visit 5 (Phone or in person visit approximately one week after Visit 4):

- You will collect a stool sample before your fifth visit. You can return it to us in-person if you have an in-person visit or you will mail it to us as soon as possible.
- You will undergo a physical examination and be asked questions about your medical history if visit is conducted in person.
- Questionnaires – you will complete eight questionnaires to look at the severity of your GI and psychological symptoms.
- You will be asked if you have experienced any adverse medical events since you last met with the study team.
- The last hydrogen breath test is conducted at this visit. You will be given a take home hydrogen breath test kit to perform the test remotely.
- Please do not take Peptobismol for at least 2 weeks before the test. You also should fast for at least 8 hours and should not smoke for at least 6 hours before the test. These restrictions will help improve the accuracy of the test.
- There should be another person available in case there a side effects of dizziness or lightheadedness. There should also be snacks readily available.
- Glucose Hydrogen Breath Test – you will be asked to drink a sugar water drink. You will then be asked to blow into a tube every 15 minutes for 2 hours to measure whether you have overgrowth of bacteria in your small intestine. The hydrogen breath test will be done remotely with a take home test kit.
- Should you choose to participate in the optional sub-study #3, you will have your blood drawn at Visit 5. A trained phlebotomist will collect 1 tube, a total of about 10mL or 2 teaspoons of blood. These blood samples will be stored for future IBS-D research. You are free to decline participation if you do not want to have your blood sample stored. You will have the ability to accept or decline separate permission at the end of this consent document.
- You will have completed your 24-hour food recall by this time.

Stool samples before, during, and after you have been on this diet will be stored for future research on IBS. You are free to decline participation if you do not want to have your stool sample stored. You will have the

ability to accept or decline separate permission at the end of this consent document. This will be listed as "Optional Sub-Study #1".

Low FODMAP Group:
Visit 1 (Phone or in person visit):
You will be asked to complete questionnaires that determine the severity of your GI symptoms and drop off/mail your stool samples, three-day food diary, and logs. We will also provide a glucose hydrogen breath test kit for you to perform at home for the duration of the pandemic. Female participants capable of bearing children or consented to the optional sub study #2 and/or #3, will have visit one conducted in-person with an approximate duration of 1.5 hours. Male participants and female participants not capable of bearing children who have not consented to optional sub study #2 and #3 will be able to conduct the visit remotely during the pandemic. You will receive low FODMAP diet consultation during this visit.

- Questionnaires – you will complete eight questionnaires to look at the severity of your GI and psychological symptoms.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements if visit is done in person.
- Urine pregnancy test – Women capable of bearing children will undergo a urine pregnancy test.
- You will meet with a nutritionist for education on a low FODMAP diet over phone or video for the duration of the pandemic. The diet plan will be individualized to you based on the information from your diet questionnaires.
- Please do not take Peptobismol for at least 2 weeks before the test. You also should fast for at least 8 hours and should not smoke for at least 6 hours before the test. These restrictions will help improve the accuracy of the test.
- There should be another person available in case there a side effects of dizziness or lightheadedness. There should also be snacks readily available.
- Glucose Hydrogen Breath Test – you will be asked to drink a sugar water drink. You will then be asked to blow into a tube every 15 minutes for 2 hours to measure whether you have overgrowth of bacteria in your small intestine. The hydrogen breath test is done remotely and you will be given a test kit to take home.
- After you complete the glucose hydrogen breath test, you will then start on a low FODMAP diet for the next 4 weeks.
- Should you choose to participate in the optional sub-study #2, you will provide a saliva sample, which will be self-collected in a provided kit. The sample size will be about 2mL, or approximately ½ teaspoon. These samples will be stored for genetic analysis related to enzymes pertaining to IBS-D and may be shared with investigators at other institutions (Karolinska Institute and IKMB Kiel) to run specialized tests. You are free to decline participation if you do not want to have your saliva sample stored. You will have the ability to accept or decline separate permission at the end of this consent document.
- Should you choose to participate in the optional sub-study #3, you will have your blood drawn. A trained phlebotomist will collect 1 tube, a total of about 10mL or 2 teaspoons of blood. These blood samples will be stored for future IBS-D research. You are free to decline participation if you do not want to have your blood sample stored. You will have the ability to accept or decline separate permission at the end of this consent document.
- You will be asked to record your stool frequency and form each day online or on paper log.
- You will also record the severity of your abdominal pain and bloating each day online or on paper log.
- You will also record your diet over a 24-hour period every week.

Visit 2 (Phone or In-Person Visit - Approximately one week after Visit 1):

- You will be asked questions about your dietary compliance.
- You will continue to record your stool frequency and form, abdominal pain and bloating online or on paper.
- You will have completed your 24-hour food recall by this time.
- You will be asked if you have experienced any adverse medical events since you last met the study team.
- You will be asked questions about your physical health and wellbeing.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements if the visit is conducted in person.

Visit 3 (Phone or In-Person Visit - Approximately one week after Visit 2):

- You will collect a stool sample before your third visit. You can return it to us in-person if you have an in-person visit or you will mail it to us as soon as possible.
- Questionnaires – you will complete eight questionnaires to look at the severity of your GI and psychological symptoms.
- You will be asked questions about your dietary compliance.
- You will also have a consultation with a U of M nutritionist via phone or video for the duration of the pandemic. They will answer any questions you have about the diet and check in on your progress.
- You will continue to record your stool frequency and form, abdominal pain, and bloating online or on paper.
- You will have completed your 24-hour food recall by this time.
- You will be asked if you have experienced any adverse medical events since you last met with the study team
- You will be asked questions about your physical health and wellbeing.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements if the visit is conducted in person.

Visit 4 (Phone or In-Person Visit - Approximately two weeks after Visit 3)**:**

- You will collect a stool sample before your fourth visit. You can return it to us in-person if you have an in-person visit or you will mail it to us as soon as possible.
- You will be asked questions about your dietary compliance.
- You will have completed your 24-hour food recall by this time.
- You will continue to record your stool frequency and form, abdominal pain, and bloating online.
- You will be asked if you have experienced any adverse medical events since you last met with the study team.
- You will be asked questions about your physical health and wellbeing.
- You will undergo a basic physical examination to measure height, weight, blood pressure, pulse, and temperature measurements if the visit is conducted in person.

Visit 5 (Phone or in person visit approximately one week after Visit 4):

- You will collect a stool sample before your fifth visit. You can return it to us in-person if you have an in-person visit or you will mail it to us as soon as possible.
- You will undergo a physical examination and be asked questions about your medical history if visit is conducted in person.

- Questionnaires – you will complete eight questionnaires to look at the severity of your GI and psychological symptoms.
- You will be asked if you have experienced any adverse medical events since you last met with the study team.
- The last hydrogen breath test is conducted at this visit. You will be given a take home hydrogen breath test kit to perform the test remotely.
- Please do not take Peptobismol for at least 2 weeks before the test. You also should fast for at least 8 hours and should not smoke for at least 6 hours before the test. These restrictions will help improve the accuracy of the test.
- There should be another person available in case there a side effects of dizziness or lightheadedness. There should also be snacks readily available.
- Glucose Hydrogen Breath Test – you will be asked to drink a sugar water drink. You will then be asked to blow into a tube every 15 minutes for 2 hours to measure whether you have overgrowth of bacteria in your small intestine. The hydrogen breath test will be done remotely with a take home test kit.
- Should you choose to participate in the optional sub-study #4, you will have your blood drawn at Visit 5. A trained phlebotomist will collect 1 tube, a total of about 10mL or 2 teaspoons of blood. These blood samples will be stored for future IBS-D research. You are free to decline participation if you do not want to have your blood sample stored. You will have the ability to accept or decline separate permission at the end of this consent document.
- You will have completed your 24-hour food recall by this time.

Stool samples before, during and after you have been on this diet will be stored for future research on IBS. You are free to decline participation if you do not want to have your stool sample stored. You will have the ability to accept or decline separate permission at the end of this consent document. This will be listed as "Optional Sub-Study #1".

As a subject participating in this research study, you have certain responsibilities that may apply to this study, such as ensuring that you arrive at all of your scheduled appointments, take your study medication as directed, and report any adverse reactions you may have during the study.

Besides the information about the main study, the following information is specific to optional sub-studies. We would like to better define the reason why patients may or may not respond to IBS-D treatments. To do this, we would like your permission to study your colon tissue (with biopsies from your colonoscopy), saliva, blood, and/or medical information. Biopsies will be used to create "colonoid" models to understand enzymes that may potentially be involved with IBS-D. Saliva will also be used to study enzymes that could be involved with IBS-D. Blood will be used to better understand immune markers that may be involved in IBS-D. You can take part in the main study even if you don't participate in any of the optional sub studies.

Optional sub-study #1: The sub-study is looking to analyze metabolomics differences from the stool samples. This sub-study aims to learn about the physical processes that lead to microbiome changes seen in IBS patients. Participants consented to this sub-study will collect a stool sample at visits 1, 3, 4, and 5. We will also collect a one-time stool sample and symptom questionnaires from healthy controls. Samples will then be stored for long-term storage.

Optional sub-study #2: This sub-study is looking to understand enzymes that may potentially be involved with Irritable Bowel Syndrome with Diarrhea. It requires a one-time collection of saliva sample on visit 1.

Optional sub-study #3: This sub-study requires blood collections to better understand immune markers that may potentially be involved with Irritable Bowel Syndrome with Diarrhea. We will collect 10 mL (approximately 2 teaspoons) of blood at visit 1 and 5.

Optional sub-study #4: This sub-study requires tissue collection. Biopsies will be taken from eligible subjects who are scheduled to undergo a colonoscopy for clinical purposes (e.g. to rule out alternative causes of symptoms or screening for colon cancer). Biopsies will be utilized to generate human intestinal enteroids to study host-microbial interactions determining response to treatment in IBS. Twelve mucosal biopsies will be obtained for research purposes in addition to any clinically indicated biopsies.

There may be risks involved in the optional sub-studies. The risks are explained in section 5.

Even if you give us permission now to keep some of your colon tissue, saliva, and blood and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your colon tissue, saliva, and blood, we may not be able to take the information out of our research. Also, if we have shared some of your colon tissue, saliva, and blood and medical information with other researchers, we will not be able to get it back.

We will not tell you the results of the analysis of your colon tissue, saliva, and or blood. Allowing us to study your colon tissue, saliva, and blood and medical information to better understand Irritable Bowel Syndrome with Diarrhea will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

4.2 How much of my time will be needed to take part in this study?
You will either come in or have a phone visit for the baseline evaluation and undergo testing which will take approximately 2.5-3.5 hours. You will then start on treatments for IBS and will report your symptoms and answer questionnaires either in person or via phone for three additional visits. Each visit will take approximately 30 minutes. During the final visit, you will undergo repeat questionnaires and glucose hydrogen breath tests which will take approximately 2.5 hours. Patients participating in the sub-study with optional saliva collection will spend approximately 1 minute providing the sample. Patients participating in the sub-study with optional phlebotomy will spend approximately 5 minutes at Visits 1 and 5 providing a blood sample. Patients who participate in sub study 2 will add approximately five to ten minutes onto their procedure length.

4.3 When will my participation in the study be over?
Once you have been on treatment for IBS for 4 weeks and have completed all of the testing. Most subjects will complete their part in the study around 5 weeks. The entire study is expected to last about 2 years.

4.4 What will happen with my information and/or biospecimens used in this study?
With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The known or expected risks are:

A). MAIN STUDY RISKS:

- Glucose Breath Hydrogen Test:
  The most common side effects (occurring in more than 10% of patients) are:
  Bloating, abdominal discomfort/pain, and passing gas/wind , nausea, fainting during/after the test, fainting spells and dizziness

- Rifaximin:
  Rifaximin is an antibiotic which may lead to bacterial resistance to other antibiotics. However, rifaximin is minimally absorbed from the GI tract and studies have shown there is low risk for bacterial resistance. In addition, studies comparing rifaximin with placebo have not shown significant differences in the rate of side effects. General antibiotics side effect, such as nausea, vomiting, diarrhea, etc may occur. Finally, oral contraception may not be as effective when taken with rifaximin.

- FODMAP:
  A low FODMAP diet may change the bacteria in our gut. However, multiple studies examining the low FODMAP diet in IBS have shown that it is both safe and effective for the treatment of IBS. However, oral contraception may not be as effective when the gut bacteria change.

B). OPTIONAL SUB-STUDY RISKS

- Stool collection (less than 1%):
  fainting at the site of the stool collection

- Saliva Collection:
  If you choose to participate in the optional sub-study for collection of saliva, there are potential risks you should be aware of. First, these samples may be shared with investigators at other centers called Karolinska Institute and IKMB Kiel. There are potential risks including loss of privacy. We will try to minimize these risks by removing any identifiable information (e.g. your name, date of birth, address, etc.) on the saliva samples. We will not share any of this information with the investigators at the Karolinska Institute and IKMB Kiel. This part of the study is optional and you do not have to agree to participate in this optional sub-study.

- Blood Collection:
  If you choose to participate in the optional sub-study for the blood collection, there are some risks you

may be familiar with. This could be pain, bruising, or lightheadedness. Rarely there could be an infection or fainting. The person drawing your blood will be trained to do that procedure and use techniques to minimize these risks.

- Risks of Colonoscopy:
  If you choose to participate in the optional sub-study for collection of tissue from your colon, there are potential risks, including bleeding, infection, or causing a hole in your intestines. However, biopsy samples are commonly taken during a colonoscopy, and is known to be safe and rarely lead to complications.

Rare side effects in less than 1%

- Risk to your privacy
- Worsening of your symptoms
- Emotional distress from completing questionnaires

The researchers will try to minimize these risks by:

In order to minimize risk from the glucose hydrogen breath test, you are free to stop at any point you experience significant pain or discomfort. You can take medications, such as simethicone or Tylenol, if you develop significant bloating or discomfort. In order to minimize risk, procedures or blood tests already being performed for diagnostic or treatment purposes will be used for this research. We will use every effort to maintain your privacy including keeping all records from this study in a secure, locked location and will only share information with other members of the study team. For the questionnaires, you may skip any question that you feel uncomfortable answering. You are free to withdraw from the study at any time.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study. However, some subjects with IBS will demonstrate improvement in their symptoms after being on rifaximin or a low FODMAP diet. Frequent and comprehensive assessment provided as part of participating in this study may allow for closer monitoring of disease course. In addition, this study may help us learn more about the possible causes and treatments for IBS.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?
You are free to decline participation in this study. We will continue to treat your IBS if you do not want to participate in this study. There may be other ways of treating your condition including anti-spasmodics, anti-depressants, antibiotics, and dietary modification. However, any alternative treatment option should be undertaken with appropriate continued medical supervision.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
There is no harm if you decide to leave early. However, if your symptoms were improving on rifaximin or a low FODMAP diet, you may experience worsening of your symptoms again.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researcher's telephone number listed in Section 10.1.
You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.
If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you will have to arrange for treatment on your own, as the study will not provide medical treatment or provide any compensation to you. You or your insurance provider will be billed for all costs of treatment for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.
By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will receive all treatments, glucose hydrogen breath testing and/or two dietary consultations free of charge for taking part in this study.
You will be paid $20 for the baseline stool samples, $10 for additional samples taken at visit 3,4, and 5 for a total of $50. These will be sent to you as HSIP payments via checks in the mail.

8.3 Who could profit or financially benefit from the study results?
No one will benefit financially.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?
Your research information will be stored in a locked cabinet and will not be made a part of your regular medical record. However, if the researcher orders any tests, the order and results may become part of your regular medical record.

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.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected

health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, Social Security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

If you choose to participate in the sub-study involving saliva samples:

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums

- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

In addition, these samples will be sent to the Karolinska Institute in Stockholm, Sweden and the IKMB Kiel in Kiel, Germany for genetic analysis of a metabolic enzyme in the small intestine. The samples will be de-identified of patient information before being sent to the Karolinska Institute and the IKMB Kiel. After their analysis the samples will be destroyed.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished

- Express a concern about the study

Principal Investigator:	Allen Lee, MD
Mailing Address:	3912 Taubman Center 1500 E. Medical Center Dr., SPC 5362 Ann Arbor, MI 48109
Telephone:	(734) 936-9454
Study Coordinator:	Almo Regazi
Mailing Address:	52 Simpson Memorial Institute 102 Observatory Dr Ann Arbor, MI 48109
Study Coordinator:	Jared Fehlman
Mailing Address:	200 Simpson Memorial Institute 102 Observatory Dr Ann Arbor, MI 48109
Telephone:	(734) 647-3635

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?
Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Sig-A

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-B

Consent/Assent for Participating in an Optional Sub-Study #1:
This project involves optional participation in a sub-study looking to analyze metabolomics differences from the stool samples. This sub-study aims to learn about the physical processes that lead to microbiome changes seen in IBS patients. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-C

Consent/Assent for Participating in an Optional Sub-Study #2:
This project involves optional participation in a sub-study that would collect a saliva sample looking to understand enzymes that may potentially be involved with Irritable Bowel Syndrome with Diarrhea. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-D

Consent/Assent for Participating in an Optional Sub-Study #3:
This project involves optional participation in a sub-study collecting blood looking to understand immune markers that may potentially be involved with Irritable Bowel Syndrome with Diarrhea. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-E

Consent/Assent for Participating in an Optional Sub-Study #4:
This project involves optional participation in a sub-study that would collect 12 colonic biopsies of normal looking mucosa from the ileum and colon. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-F

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____