INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Principal Investigator **Sayuk, Gregory S., M.D.** PI's Phone Number **(314) 747-2954**
Last First Credentials

Title of Project: **Influence of Somatization on Central Pain Responses in Irritable Bowel Syndrome: The Modulation of Cerebral Pain Responses Using Desipramine in the Treatment of Irritable Bowel Syndrome (IBS)**

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take the time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Why is this study being done?

Individuals with irritable bowel syndrome (IBS) may experience abdominal pain as a result of pain signals in the bowel and how these signals are processed in the brain. Studies using brain imaging (pictures) have shown that IBS patients with more pain diagnoses (i.e. fibromyalgia or muscle/tissue pain, migraines, etc.) have greater activity in the regions of the brain responsible for the emotional and thought processing of pain signals. This could possibly make bowel sensations and bowel difficulties feel abnormal or more noticeable, in turn causing more severe IBS symptoms. The purpose of this protocol is to explore the role of pain diagnoses ("somatization") and their affect on brain activity in IBS patients. We will also examine the use of a medication, despiramine, which is known to affect these brain regions, in IBS patients.

This study will enroll 40 female IBS patients with and without somatization and 20 healthy controls.

Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

What am I being asked to do?

All procedures are for research purposes.

Initial Visit:
During this visit, a trained clinical interviewer will ask you a series questions. This will take about 90-120 minutes to complete. This interview will explore your medical and emotional history. Information regarding your complete medical and psychiatric history will help Dr. Sayuk and/or colleagues decide upon your candidacy for this study. Vital signs (blood pressure), cardiac ECG (a test that records the

electrical activity of the heart), and a complete blood count (requiring 1 teaspoon or 5 ml of blood drawn from a vein in your arm) will also be taken to assess whether you are eligible to participate in the study. There is a possibility that following this visit you may not be eligible to continue with further components of the study. If eligible, you will be schedule to return on another date for the fMRI. Prior to this visit, several additional brief questionnaires regarding your personal experience of physical and emotional symptoms, as well as dietary intake, will be mailed to you to complete and bring with you the day of your fMRI visit. These questionnaires will take about 20 to 30 minutes of your time to complete.

fMRI Visit:
Prior to your fMRI (described below), we will be performing a test to determine your threshold for pain. We will squeeze your left thumbnail for 40 seconds using a small pressure delivery device ("dolimeter") and ask you to determine your level of "moderate" discomfort. We will apply this amount of pressure during the actual fMRI. You will also be asked to complete two questionnaires regarding your current mood and bodily pain experiences. These will only take approximately 10 minutes to complete.

This portion of the study also involves the performance of an fMRI scan to assess your brain's activity in areas important to processing IBS symptoms. The fMRI scanner uses strong magnets to take pictures and measures how your brain looks (anatomy) and works (functions). You will be required to lie as still as possible on a padded table in the scanner for approximately 60 minutes during the study: the first 30 minutes the fMRI takes brain measurements, and the second part is the brain stimulation or functional part of the test.

During the fMRI test, a small deflated balloon will be inserted into your rectum to mimic (behave like) your IBS symptoms during the brain scan. Dr. Sayuk will prepare you for the mildly uncomfortable fMRI test by instructing you about this rectal stimulus. Before the scheduled test, if you wish to use a "Fleets enema" to cleanse your rectum, it can be provided. This cleansing is not a necessary part of the fMRI, however, if you want it you may do so. While using a jellied lubricant, Dr. Sayuk will place a soft deflated 1/2 inch wide by 3.5 inches long balloon inside your rectum. The purpose of inflating this balloon during the fMRI scan is to observe how your brain reacts to IBS symptoms of pressure. As mentioned previously, a small pressure delivery device ("dolimeter") will also be attached to your left thumb. It will apply a mildly uncomfortable pressure to your thumb randomly during the fMRI scan. You are asked to try and keep your eyes closed during the inflations of the balloon.

Stool Sample
We request a small amount of fresh stool from you when you have a bowel movement in order to assess the microbiota (bacterial) profile of the sample.. You will be given a sterile stool sample collection container and sterile tongue depressors in order to obtain the sample. This will be collected during one of your visits.

Genetic Sample
You will be asked to submit a saliva sample into a plastic container for genetic analysis. This sample will be a one-time sample and you will not be asked to submit anymore DNA for the duration of the study.

Part of this sample will be used for current studies examining genes and proteins that may differ in people. Their clinical importance is not known at present. You will not hear from us unless we find information that may be clinically relevant. Your DNA sample will be stored in Dr. Rodney Newberry's laboratory and only Dr. Sayuk and Dr. Newberry will have access to your genetic data.

May I use your DNA sample for future research and share it with other investigators?
I would like to use the DNA sample from this study for other future research projects studying genetics. If you agree, this would mean that your genetic sample may be used for studies going on right now as well as studies that are conducted indefinitely in the future. Your DNA sample may be used to develop investigational test, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration.

I would also like your permission to share you DNA sample with other investigators doing research in similar fields (gastroenterology and psychiatry). These investigators may be at Washington University or at other research centers. When I share the DNA sample, it will not have your name on it, only a code number, so the people who receive it will not know your name or which DNA sample is yours.

The only risk of future use or sharing the tissue and/or data is a breach of confidentiality. This means that someone might be able to identify which of the DNA samples is yours. Because I will use a code number when I am working with the DNA sample and also when I share the DNA sample, this risk is low.

You won't experience any medical or financial benefit from us using or sharing your DNA sample. By agreeing to participate, you make a free and generous gift of your DNA sample for research that might help others. This research might create new tests, treatments, or cures. If it does, you will not get any money or ownership rights to these products.

If you do decide to let us use and share your DNA sample, you can change your mind at any time. When you withdraw your consent, all DNA samples will be anonymized so that no one (including me) will ever be able to link your name to the tissue and/or data. Any research results already generated from your DNA sample cannot be destroyed or recalled.

Letting us use and share your DNA sample is voluntary. You do not have to agree to the sharing and future use of your tissue and/or data in order to participate in the main part of this study.

_____Yes (Initial here if it is okay for us to store/share your DNA sample as described above.)

_____No (Initial here if you do not want us to store/share your DNA sample as described above.)

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining functional magnetic resonance images (fMRI) of your brain. By agreeing to be part of this study you give up any property rights you may have in the functional magnetic resonance images (fMRI) of your brain. We would like to use your fMRI for other research projects in the future. These future studies may provide additional information that will be helpful in understanding IBS but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your fMRI might be used to develop tests, treatments or cures. There are no plans to provide financial compensation to you should this occur. If you agree, this means we will store your fMRI and may use it for studies going on right now as well as studies that are conducted in the future.

Your data may be used to develop investigational test, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration.

I would also like your permission to share your fMRI with other investigators doing research in similar fields such as gastroenterology, neurology, otolaryngology, and psychology. These investigators may be at Washington University or at other research centers. We may also share you research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

Your fMRI will be stored without your name or any other kind of link that would enable us to identify which sample(s) or data are yours. Therefore, if you give permission to store and use your fMRI, it will be available for use in future research studies indefinitely and cannot be removed.

Please place your initials in the blank next to Yes or No for each of the questions below:

My data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My data may be shared with other researchers and used by these researchers for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

If you were enrolled as a healthy control, you will return in four weeks for a repeat of the fMRI.

Otherwise, all 40 IBS patients will receive an active tricyclic antidepressant, despiramine (DES), following the completion of your fMRI and continue to take it for 4-weeks. You will begin taking 25 mg. of desipramine (DES) daily in the evening. [The study medication will be in the form of pills to be taken orally.] You will return for four subsequent follow-up visits (described below) and the dose will increase as long as you are not having side effects from the medication. Medication may be increased up to a maximum of 100 mg. per day. All doses will be dispensed by the Barnes-Jewish Hospital (BJH) pharmacy.

Treatment Visits: Weeks 1, 2, 3
Any medication you have taken since last visit will be reviewed, as well as any problems you may have had since last visit will be discussed. You will be asked to complete questionnaires regarding your current IBS symptoms. These questionnaires will be administered in a strictly confidential manner, and will take about 20 to 30 minutes of your time to complete. Any unused study medication will be collected, and you will be provided more medication based on review of your current dose.

Week 4: Completion of Treatment Arm
During this visit, a trained clinical interviewer will once again ask you a series questions. This will take about 90-120 minutes to complete. This interview will explore your demographic, medical, and emotional history. You will also be asked to complete questionnaires regarding your current IBS symptoms. These questionnaires will be administered in a strictly confidential manner, and will take about 20 to 30 minutes of your time to complete. You will also be scheduled for a repeat fMRI scan. This will require approximately 60 minutes. The procedure with Dr. Sayuk using the rectal stimulation with the balloon insertion is identical to the fMRI that you experienced in the beginning of this study.

Once the study is completed, based on your symptom responses, you will have the opportunity to continue the use of the study medication as your IBS maintenance management. A one-month supply of this medication will be made available free-of-charge at the conclusion of participation to allow transition of care back to your primary care doctor.

Data Collected From Your Medical Record
The research team may access the following sources of your health information to conduct the study: Hospital/physician medical records, Lab, pathology and/or radiology results, Biological specimens *(including blood),* Physiologic Imaging *(Diagnostic or Non-diagnostic), and* interviews/questionnaires.

How long will I be in the study?
If you agree to take part in this study, your involvement will last for approximately four weeks. Your participation ends after the final fMRI scan.

How many other participants will be in the study?
60 participants will be recruited for this study at Washington University.

What are the costs?
You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address if a check will be mailed to you. The checks will be mailed after authorization through the payment mechanism in Dr. Sayuk's department, and may take 2 weeks to process. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

You will be paid for your time and travel expenses incurred because you joined this study. You will receive up to $400.00 for your time, as well as free parking. You will receive $150 after completion of the first fMRI, $100 after completion of the drug treatment phase, and another $150 upon completion of the final fMRI.

What are the risks?
You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Some risks described in this consent document, if severe, may cause death.

Interview and questionnaires:
Likely: The questions on forms and in interviews may be viewed as very personal, having to do with bowel habits and feelings. You may possibly feel emotionally uncomfortable discussing feelings related to your IBS and their emotional well-being. If you feel uncomfortable during the interviews, you may choose not to answer the questions or ask the research staff for an explanation of the rationale for the questions. You may refuse to answer any questions that you are not comfortable answering.

Rectal balloon and dolorimetry testing:
Likely: Embarrassment during balloon placement may be experienced; however, the physician performing the rectal balloon placement is aware of this possibility and will respect your privacy and maintain your comfort to the extent possible. You will feel various levels of rectal distention during inflation of balloon. The P.I. will fully explain the sensations and demonstrate the distension by using an actual 5 cm. by 9 cm. balloon prior to insertion in the rectum. You will also feel discomfort on your left thumb with activation of the dolimeter. This is usually brief and you will have the opportunity to determine this pressure prior to the fMRI.
Less likely: Tenesmus post-testing. You will feel an uncomfortable mild rectal fullness after testing is completed which usually goes away within a few minutes. You may experience small amount of stool incontinence or flatus during or immediately after the balloon testing. Bathrooms are readily available for use immediately following the procedure.
Rare: You could possibly experience mild rectal bleeding during or after the balloon distention. Rectal tears have never been reported in the medical literature to date despite hundred of participants enrolled in studies using balloon distensions; however it theoretically remains a possible rare result of rectal distension. Syncope ("fainting") is a rare possible result of rectal pressure caused by the balloon. Some people have fainted while experiencing a large hard stool that puts pressure in the rectum and the nerves lining the rectum. The rectal pressure used for this study, although within

standard IBS testing limits, could possibly result in rectal nerve stimulation and lead to "vasovagal response" (i.e., fainting or an irregular heart beat) requiring medical intervention. The study physician is present during balloon distention and there is a full Barnes Jewish Hospital emergency team available should it be necessary to stop the imaging and treat the symptoms of vasovagal stimulation. You should communicate any uncomfortable physical symptoms experienced during balloon distention with the study staff.

Risks associated with the fMRI scan:
You may be uncomfortable inside the MRI scanner if you do not like to be in closed spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system. You can tell them to stop the scan at any time.

The MRI scanner produces a loud hammering noise, which has caused hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.

If you have a device such as a pacemaker, bone hardware, or device placed in your uterus there may be additional risks. We will review what device you have and inform you of these risks. In general, these risks could be:

- heating or movement of the device
- device malfunction
- damage to the tissue that surrounds the device.

If you have a skin tattoo, including cosmetic tattoos (eye-liner, lip-liner) you could experience the following:

- irritation, swelling or heating in the area of the tattoos
- in rare instances a primary or secondary burn.

If you have a tattoo we will offer you a cold, wet washcloth to put over the tattoo to reduce this risk.

Medication
Antidepressant medications are used to treat a variety of conditions, including depression and other mental/mood disorders. These medications can help prevent suicidal thoughts/attempts and provide other important benefits. However, studies have shown that a small number of people (especially people younger than 25) who take antidepressants for any condition may experience worsening depression, other mental/mood symptoms, or suicidal thoughts/attempts. Therefore, it is very important to talk with the doctor about the risks and benefits of antidepressant medication (especially for people younger than 25), even if treatment is not for a mental/mood condition.

Tell the doctor immediately if you notice worsening depression/other psychiatric conditions, unusual behavior changes (including possible suicidal thoughts/attempts), or other mental/mood changes (including new/worsening anxiety, panic attacks, trouble sleeping, irritability, hostile/angry feelings, impulsive actions, severe restlessness, very rapid speech). Be especially watchful for these symptoms when a new antidepressant is started or when the dose is changed.

The potential side effects with the administration of desipramine are:
Likely: dry mouth, vision problems, constipation and mild inability to urinate
Less Likely: light headedness, drowsiness, increased perspiration and mild tremors as well as insomnia.
Rare: potentially life-threatening abnormal beating of the heart

Stool Sample
There is no risk associated with providing a stool sample.

Blood Drawing
The blood draw may cause bleeding, bruising, or pain. Some people become dizzy or feel faint. There is also a rare risk of infection.

ECG (Electrocardiogram) Testing
There is a rare risk of a local skin reaction to the adhesive used on the ECG skin pads.

Genetics
There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans and employers with greater than 15 employees to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance or long term-care insurance.

Breach of Confidentiality
One potential risk of participating in this study is that confidential information about you might be accidentally disclosed. We will do our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the Confidentiality section of this consent form for more information.

Pregnancy/Childbearing Potential

If you are a woman of childbearing potential, please read.

Some parts of this study might cause physical or mental problems in an unborn baby. In addition, if you are or become pregnant, this study may involve risks to your embryo or fetus, which are currently unforeseeable. You must tell the doctor immediately if there is any chance you are pregnant. You must also tell the doctor if your birth control method fails while you are on the study.

To take part in this study, you must have a pregnancy test before starting the study. You must use an acceptable method of birth control and must not become pregnant.

Please discuss with your research physician how long you need to wait before becoming pregnant.

What happens if you are injured because you took part in this study?
Washington University investigators and their staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator (314-454-8201) and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you have had to seek medical care for a research-related injury, please notify the investigator as soon as possible.

Are there benefits to taking part in the study?
You may or may not benefit from being in this study.
However, we hope that, in the future, other people might benefit from this study because information from this study will further the medical community and society's understanding of IBS and its treatment.

What other options are there?
Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. You may withdraw by telling the study team you are no longer interesting in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu/participants/ under Withdrawing from a Research Study. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

Other than not taking part in the research, you may: seek medical care from your private doctor.

How will you keep my information confidential?
We will do everything we can to protect your privacy. The information you give us will be given a code number. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and his research team will be able to see the list. We will protect your information, but there is a chance somebody might see it.

Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- The National Institutes of Health (NIH)
- Hospital or University representatives to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health insurance company. This information may also be released as part of a release of information request.

- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form.

The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
  - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu/participants//withdrawing-from-a-study/ or you may request that the Investigator send you a copy of the letter.

- **If you revoke your authorization:**
  - The research team may only use and share information already collected for the study.
  - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
  - You will not be allowed to continue to participate in the study.

Please specify any contact restrictions you want to request for this study only.
(Example – no calls at home, no messages left for you, no emails, etc.) **No Restrictions_____**
_____
_____

Whom do you call if you have questions or problems?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- 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: Gregory S. Sayuk, MD
Mailing Address: Washington University School of Medicine, Division of Gastroenterology, Campus Box 8124, St. Louis, MO 63110
Telephone: 314-747-2945

If you wish to talk to someone else, or have questions or concerns about your rights as a research participant, call of Washington University's Human Research Protection Office (WU HRPO) at r 1-(800)-438-0445.

The Principal Investigator (PI) may withdraw you from the study without your consent if considered appropriate, for example, if you are not able to follow the treatment schedule or you begin taking a medication that should not be used with the study medication. It may be in your best interest to allow follow-up outside the study. The PI will share any new information that could change how you feel about continuing in the study.

You may choose not to take part in this research study or you may withdraw your consent at any time. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

FOR IRB USE ONLY

IRB ID #: 201102251
APPROVAL DATE: 07/15/22
EXPIRATION DATE: 07/14/23

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 07/14/23.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)