INFORMED CONSENT FORM

Official Title: A Probiotic Intervention to Prevent Relapse Following Hospitalization for Mania

NCT Number: NCT03383874

IRB Approved Date: March 18, 2024

The University of Texas Southwestern Medical Center
Parkland Health & Hospital System
Children's Medical Center
Retina Foundation of the Southwest
Texas Scottish Rite Hospital for Children
Texas Health Resources
John Peter Smith Health Network

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: A Probiotic Intervention to Prevent Relapse Following Hospitalization for Mania

Funding Agency/Sponsor: Stanley Medical Research Institute

Study Doctors: E. Sherwood Brown, M.D., Ph.D.

If you are a Dallas patient, you may call these study doctors or research personnel during regular office hours at 214-645-6950. At other times, you may call them at 214-648-5555.

If you are a JPS patient, you may call these study doctors during regular office hours at 817-702-8561.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask them to explain any words or information that you do not clearly understand. The purposes of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
This study is being done to determine if adding a probiotic to your regular treatment can reduce the chances of being readmitted to hospital for psychiatric concerns.

Why is this considered research?
This is a research study because this probiotic is investigational and has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of mania or bipolar disorder.
The following definitions may help you understand this study:

- Double-blind means neither you nor the researchers will know which study medication you are receiving.
- Placebo-controlled means that some participants will get a placebo. A placebo looks like the investigational medication but it includes no active ingredients.
- Randomization means you will be placed by chance (like a flip of a coin) in one of the study groups.
- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.

- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals or at John Peter Smith Health Network in Fort Worth.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you were admitted to the hospital for symptoms of mania.

Do I have to take part in this research study?
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study, it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?
About 46 people will take part in this study at UT Southwestern, Parkland Health & Hospital System, and Texas Health Resources (Texas Health Recovery and Wellness Center, Texas Health Arlington Memorial Behavioral Health, Texas Health Seay Behavioral Health Plano, Texas Health Springwood Behavioral Health Hospital HEB). This study is also taking place at another medical facility in the country (JPS Health Network, Fort Worth, TX), and 20 patients will be enrolled at JPS. There will be 66 people enrolled in this research study throughout Dallas, TX and Fort Worth, TX.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

Screening Procedures
To help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:
- Physical exam and medical history
- Psychiatric evaluation
- Vital signs
- Blood tests
- Demographic information (age, sex, ethnic origin)

Group Assignment
If the researchers believe you can take part in this study, you will be assigned randomly (like a flip of a coin) to receive either a probiotic or placebo (inactive substance). You have a 1 in 2 chance of receiving the probiotic or placebo.

The group you will be in is decided by a statistician. Neither you nor the researchers will be allowed to choose which group you are assigned to.

Study Medication/Intervention

If you decide to participate in this study you will take either:

- capsules containing approximately 10^8 (100,000,000) colony forming units of the probiotic organisms, Lactobacillus GG and Bifidobacteria lactis strain Bb12
- a placebo, an inactive substance which looks identical to the study medication

Procedures and Evaluations during the Research

	Baseline	Week 0	Weeks 1 -3	Week 4	Weeks 5-7	Week 8	Weeks 9-11	Week 12	Weeks 13-15	Week 16	Weeks 17-19	Week 20	Weeks 21-23	Week 24
SCID	X													
Physical Exam & Psych Eval	X													
Blood draw, stool collection, urine collection	X							X						X
Height (BL only), Weight, and Vitals, Clinician Follow-up	X			X		X		X		X		X		X
Tx &/or Hospitalization, ISS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Compound		X		X		X		X		X		X		X
New Mood Episode		X	X	X	X	X	X	X	X	X	X	X	X	X
BPRS, YMRS, MADRS, QLESQ, CSSRS, CGI-BP	X			X		X		X		X		X		X
TMT, IGT, RAVLT, Stroop	X							X						X
TII	X													
Sheehan Disability Scale	X							X						X
Dietary Questionnaire	X							X						X
Exit survey														X

Baseline Visit (~3-3.5 hours): You will complete these assessments to determine your eligibility to be in the study. The Structured Clinical Interview for DSM-5 (SCID) will determine your psychiatric diagnosis. You will also receive a psychiatric evaluation and provide information on your background including age, race, gender, years of education, your psychiatric and medical history, and your current medications. The Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Clinical Global Impression for Bipolar Disorder (CGI-BP), the Internal State Scale (ISS), and the Brief Psychiatric Rating Scale (BPRS) will determine your current mood status. The Columbia-Suicide Severity Rating Scale (C-SSRS) will determine any suicidality that you may be experiencing, and your quality of life will be assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) and the Sheehan Disability Scale. Your current ability to complete cognitive tasks will be assessed by the Trail Making Test (TMT), the Iowa Gambling Task (IGT), Stroop task, and the Ray Auditory Verbal Learning Test (RAVLT). The Treatment Impression Inventory (TII) will

evaluate your views and feelings about medical treatment. An assessment of your dietary intake for the past 24 hours will be conducted.

A blood sample of a little over two tablespoons will be drawn to determine your physical health and also for immune markers which we are investigating in this study. A urine sample will also be collected for a drug screen, a pregnancy test (if applicable), an additional check on your physical health and a later analysis of immune markers. A throat swab will be collected to examine the bacteria which live in your throat and a stool specimen will be collected to examine the bacteria which live in your gut. (These stool specimens can be collected in the privacy of your own home and then returned to the clinic within 1 week of your in-person visit). A psychiatric assessment, a physical exam, and collection of height, weight and vitals will be done. We will request your consent to contact your outpatient treatment providers to inform them of your participation in this study and establish communication with your normal treatment providers. We will also ask to obtain your hospital admission record to determine the reason for your admission to the hospital.

Week 0: Once you are considered eligible to participate in the study, you will come in to receive your study compound. The coordinator will ask about any changes to your medications, current treatment or any re-hospitalizations. You will also complete the Internal State Scale (ISS) to determine your mood.

Weeks 1-3, 5-7, 9-11, 13-15, 17-19, 21-23, Phone calls (~20mins): The research coordinator will call you on the weeks in between your in-person visits to collect reports of any adverse events, including a current pregnancy, how well you are taking your study medication, changes and status on your current treatment and any re-hospitalizations, updates to your medication list, and brief assessment of your current symptoms to confirm your current diagnosis. We will also provide you a link to complete the ISS via an online web application called the REDCap System.

Weeks 4, 8, 16, and 20, Virtual visits (~1hr): During these virtual visits, we will collect reports of any adverse events, including a pregnancy, updates on your current treatment and medications and we will note any re-hospitalizations, pill counts and/or your report of how well you are taking your study medication. A brief assessment of your current symptoms to confirm your current diagnosis, and other assessments will be done. These include an evaluation of your current mood using the Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression for Bipolar Disorder (CGI-BP), and the Internal State Scale (ISS). Your quality of life will be assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ), and any suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (CSSRS). Your weight and vitals will also be collected, and you will meet with a psychiatry clinician for a brief evaluation.

Weeks 12 and 24, In-person visits (~2hrs): At these in-person visits, we will collect reports of any adverse events, including a pregnancy, updates on your current treatment and medications and we will note any re-hospitalizations, pill counts and/or your report of how well you are taking your study medication. A brief assessment of your current symptoms will be done to confirm your current diagnosis and other assessments will be done. These include an evaluation of your current mood using the Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), Clinical Global

Impression for Bipolar Disorder (CGI-BP), and the Internal State Scale (ISS). Your quality of life will be assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ), and the Sheehan Disability Scale, and any suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (CSSRS). Assessment of your current cognitive abilities will be done using the Trail Making Test (TMT), the Iowa Gambling Task (IGT), Stroop task, and the Ray Auditory Verbal Learning Test (RAVLT). An assessment of your dietary intake based on a 24 hour recall of food intake will also be collected. Blood of a little less than one and a half tablespoons, a urine sample, a throat swab, and a stool specimen (which can be collected at home and returned to the clinic) as well as weight and vitals will also be collected. You will meet with a psychiatrist for a brief evaluation. At week 24 (or your last study visit if you decide to stop your study participation early), you will also complete an exit survey regarding your perception of in-person vs. virtual research visits.

Follow-up Phone Call, 6 months following study completion (~15 min): The coordinator will call you and collect information about any (re)hospitalization you may have had, any current treatments you are undergoing. You will be asked to complete the Internal State Scale (ISS) via the REDCap online link and you will be asked to complete the Columbia Suicide Severity Rating Scale (CSSRS) over the phone.

The assessments in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at your assessments to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can then decide together whether to follow up with more tests or treatment. Because the assessments done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

Procedures for storing of extra or left over samples

Dr. Brown, who is the Principal Investigator of this study overall, will keep your remaining samples in a research laboratory at the UT Southwestern Medical Center or at a study collaborator's laboratory at Johns Hopkins University until they are all gone, become unusable or until Dr. Brown decides to discard the samples.

How long can I expect to be in this study?

The study starts with your baseline visit and continues for 24 weeks once you start your study medication.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Study Procedure/Intervention

Because of your participation in this study, you are at risk for the following side effects. Please understand that the risks listed are for over-the-counter probiotics; however, those you are taking for this research study may be a larger dose than is sold in drug or health food stores. Therefore, the risks you may experience may be more severe than those listed below. Please contact your study doctor if you have any questions. You should discuss these noted effects with the researchers and your regular health care provider.

The probiotic may cause some, all or none of the side-effects listed below.

Frequent
- Gas
- Bloating
- Stomach discomfort

Uncommon
- Allergic Reaction/Rash

Psychological Stress
Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks of Blood Drawing
Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

You will have about one and an a half to a little over two tablespoons of blood (depending on the visit) collected at three different visits because you are in this research study.

Placebo
If you receive a placebo, you will not receive active medication for your health problem. If your problem becomes worse, your participation in the research will stop. If this happens, your study doctor can discuss alternative care with you.

Other Risks
There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?
You will be closely monitored for any signs of side effects, and most of the known risks of probiotics are very mild. Your current mood status and changes in your treatment will also be monitored regularly. If you experience serious complications in your condition during the study, such as active suicidal or homicidal ideation, the study team will follow through with our standard procedures for getting you seen by medical professionals who can assess your psychiatric status. If you develop a severe or life-threatening medical condition, a pregnancy, or withdraw your informed consent, your study participation will be discontinued and you will be provided with referrals for appropriate care. All female participants of childbearing age at the time of enrollment will be given a pregnancy test and at any time during the study in the case of a suspected pregnancy. In case of pregnancy, study medication will be immediately discontinued and the Principal Investigator will discuss alternative treatment choices with you. Urine drug screens will also be collected at regular intervals throughout the study at any time if drug use is suspected. If you have a positive drug test and then a subsequent second positive

drug test, you will be discontinued from the study.

What will my responsibilities be during the study?
While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Store study capsules in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Carry information about the probiotic in your purse or wallet.
- Report to the researchers any injury or illnesses while you are in the study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?
If you agree to take part in this study, there may be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research. Previous research with this probiotic suggested a reduced chance of being readmitted to the hospital for psychiatric symptoms. This study is designed to see if this benefit can be also be seen in another group of patients like yourself.

We hope the information learned from this study will benefit others with manic symptoms in the future. Information gained from this research could lead to better treatment for mania and bipolar disorder.

What options are available if I decide not to take part in this research study?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- Receive pharmacological treatment for your condition from a provider of your choice
- Receive psychiatric treatment (e.g., counseling) for your condition from a provider of your choice
- You have the choice of receiving no treatment at all

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?
Yes. You will be paid according to the following schedule:

- $40 for completion of the baseline visit.
- $40 for completion of Week 0.
- $10 for completion of each phone contact at Weeks 1-3, 5-7, 9-11, 13-15, 17-19, and 21-23; (total $180).
- $30 for the completion of each in-person visit at Weeks 4, 8, 16, and 20 (total $120).
- $80 for the completion of in-person visits at Weeks 12 and 24 due to the additional lab work and assessments (total $160).
- $50 as a completion bonus at the completion of the Week 24 visit.
- The total compensation which can be received by those who complete all study visits will be $590.

DART day passes will be available to Dallas patients if you need them for transportation to and from the appointment. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

JPS patients will receive a transportation allowance of $.54/mile to and from their homes if they drive to study visits, or a taxi voucher if they need help with transportation.

How will I be paid?
Dallas patients will be issued a UT Southwestern Greenphire ClinCard, which can be used as a credit or debit card and will receive instructions on how to use the card. JPS patients will be paid by check. Usually, these checks will be mailed out a week or two after each visit.

In order to receive study payments, your name, address, date of birth and Social Security Number (SSN) will be collected from you by the research staff. All information will be stored in a secure fashion and will be deleted once the study has been completed.

Important Information about Study Payments
1. Your SSN is needed in order to process your payments. Should you decide not to provide your SSN, your study participation payment will be decreased at the current IRS tax rate. Study payments are considered taxable income and are reportable to the IRS.
2. An IRS Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.
3. Your payment information will not be shared with any third parties and will be kept completely confidential

This information will remain confidential unless you give your permission to share it with others, or if we are required by law to release it.

If you are a Dallas study patient, you should know that UT Southwestern, as a State agency, will not be able to make any payments to you for your participation in this research if the State Comptroller has issued a "hold" on all State payments to you. Such a "hold" could result from your failure to make child support payments or pay student loans, etc. If this happens, UT Southwestern will be able to pay you for your taking part in this research 1) after you have made the outstanding payments and 2) the State Comptroller has issued a release of the "hold."

If you are an employee of UT Southwestern, your payment will be added to your regular paycheck and income tax will be deducted. JPS employees will receive the same form of payment as any other JPS study patient.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or Parkland Health & Hospital System, Texas Health Resources (Texas Health Recovery and Wellness Center, Texas Health Arlington Memorial Behavioral Health, Texas Health Seay Behavioral Health Plano, Texas Health Springwood Behavioral Health Hospital HEB), or the John Peter Smith Health Network.

You retain your legal rights during your participation in this research.

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern or JPS staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center or at JPS, your status will not be affected in any way.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?
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.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your research record. The information included in your research record will not be available to health care providers or authorized persons, including your insurance company.

You should know that certain organizations that may look at and/or copy your research records for research, quality assurance, and data analysis include:

- Stanley Medical Research Institute
- JPS Health Network
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people
- The UT Southwestern Institutional Review Board
- The laboratory of Robert Yolken, based at Johns Hopkins University

Are there procedures I should follow after stopping participation in this research?
Yes. If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Return any unused study materials, including empty containers.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Whom do I call if I have questions or problems?
If you are a Dallas study patient and have questions about the study, contact Dr. Brown at 214-645-6950 during regular business hours and at 214-648-5555 after hours and on weekends and holidays. If you are a JPS study patient and have questions about the study, contact Dr. Claassen at 817-702-8561 during working hours.

For questions about your rights as a research participant, contact the UT Southwestern

Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

_____

Name of Participant (Printed)

_____ _____ _____ AM / PM

Signature of Participant Date Time

_____

Name of Person Obtaining Consent (Printed)

_____ _____ _____ AM / PM

Signature of Person Obtaining Consent Date Time