Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to participate in a research study of patients with mood/psychosis disorders with a co-existent metabolic health abnormality. We hope to implement and learn whether the low-carbohydrate high-fat (LCHF) ketogenic diet is effective in improving metabolic and mental health in a cohort of outpatients with bipolar disorder or schizophrenia. A ketogenic diet is a diet in which carbohydrates are lowered to the point in which your body uses ketones for energy (called nutritional ketosis) and helps burn fat more effectively. You were selected as a possible participant in this study because you have been diagnosed with either bipolar disorder or schizophrenia and identified by your physician to have a metabolic or weight abnormality.

If you decide to terminate your participation in this study, you should notify Dr. Shebani Sethi at 650-721-4419.

This research study is looking for 20 participants with bipolar disorder or schizophrenia (10 with bipolar disorder and 10 with schizophrenia) with a weight or metabolic abnormality. Stanford University is the only site participating in this study. We expect to enroll 20 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

If you choose to be a part of this study, your participation is expected to last up to about 16 weeks and will require about 10 appointments, either visits to the study site or remote visits, along with an initial assessment screening and dietary teaching.

If you are coming in-person to research visits, you are required to be fully vaccinated—2 doses (1 for Johnson and Johnson), 2 weeks out and to provide proof of your vaccination (e.g., CDC COVID-19 Vaccination Card, e-Health

record, etc.) to the researcher prior to study participation. Alternately, you can provide a negative COVID test within 72 hours of your visit.

Remote patients will do initial assessment screenings including blood draws and body composition measurements at locations within a 90 minute drive of their home, requiring additional separate visits for completion. Remote patients may complete dietary teaching by watching a video.

PROCEDURES

The ketogenic diet (low-carbohydrate, high fat) intervention is specifically for research and not currently part of routine clinical care. If you choose to participate, Dr. Sethi and her research study staff will set up an initial screening assessment. The initial screening assessment will take place with an in-person, telephone call, or remote video conference screening; and consultation with the PI totaling 45 min – 1 hour. Patients will be evaluated by Dr. Sethi to obtain pertinent psychiatric and medical history. Through these various means, inclusion and exclusion criteria will be assessed.

If you meet eligibility, you will be invited to meet with our research coordinator in person, by telephone or by HIPPA secure video conferencing, to go over all study procedures, visit timelines, and consent forms. Your height, weight, blood pressure, body fat mass (the amount of fat in one's body), waist circumference and heart rate will be measured by staff or self-reported and a set of labs ordered for participant to obtain. If you decide to do appointments virtually, you will report vitals and measures to the doctor. These baseline lab tests include: Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), advanced lipid panel, hemoglobin A1c (HbA1c), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and high sensitivity C-Reactive Protein (CRP). A total of 8 vials (4 vials at the start of study and 4 vials at the end of study) of blood will be collected in the study (estimated 48-60ml). At the same meeting, participants will check-in with Dr. Sethi to follow-up on any questions raised in the assessment measures, etc. In person appointments will include time to teach the diet, while remote appointments may be directed to watch an instruction video. Assessment measures include: Clinical Mood Monitoring (CMS), Clinical Global Impression-Schizophrenia (CGI-SCH) Scale, Clinical Global Impression for Bipolar Disorder-Overall Severity (CGI-BP-OS), Global Assessment of Functioning (GAF) Scale, Manchester Short Assessment of Quality of Life (Mansa), Brief Psychiatric Rating Scale (BPRS).

Your height will be measured at Visit 1. Your weight, height, blood pressure, heart rate, waist circumference will be measured at each visit. You will be asked to visit a facility with measuring equipment near your home in order to obtain body composition measurements and body fat mass (the amount of fat in one's body) for remote visits for a baseline reading and four further times during the study. Body composition is a term that describes the percentage of fat, muscle, water and bone found in the human body. To measure body composition, you will be required to stand on a scale (the same one used for weighing you) with no shoes or socks, and hold some special handles. If you have a pacemaker or a prosthesis that uses any other type of battery-powered or electrical power implant, you should not take part in the body composition measurement.

You and your doctor will fill out psychiatric symptom and mood evaluations monthly during the study. You will attend ten 30- minute visits through the course of the trial as described below. If you decide to do appointments virtually, you will measure and report vitals and measures to the doctor, and report body composition scan results from the facility near your home. Virtual visits will take place over Stanford Zoom in the same frequency and time of the in-person visits. Any vital measurements will be self-reported by participants over the virtual visit. Any participant can choose to do a virtual session or all virtual sessions (provided they have access to blood pressure cuff, ketone meter, and weight scale). With advance notice, necessary supplies to do measurements during remote visits will be sent to your home so they are readily available. During the first month of study entry, you will meet with Dr. Sethi weekly for a total of 4 visits. During month two, three, and four, participants will have two follow-up visits during the month totaling a total of 10 visits. The entire study thus will include 10 visits, additional body scan visits for remote participants, where the initial assessment screening and dietary teaching (visit 0) will include a visit to a laboratory near your home for a blood draw for remote participants. The 10 visits will take place over a 4- month period.
Your samples will be sent outside of Stanford for analysis at Quest Labs if you choose to conduct labs outside of Stanford.

Any samples left over when the study is completed will not be saved for future research.

<u>Women of Childbearing Potential</u>
If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently

breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to choose the appropriate option:

1) have a pregnancy test done before beginning this research study
OR

2) begin the study after the onset of your next menstrual period. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Follow the treatment plan.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Keep your diaries, food log as instructed.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Shebani Sethi at 650-721-4419.

If you withdraw from the study, or the study treatment is stopped for any reason,

- Please contact the PI directly and clearly state the reason for discontinuation.
- All study-related materials must be returned.
- There are no anticipated medical sequelae with an early termination.

The Protocol Director may also withdraw you from the study and the study program may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

- As with any weight loss program, there are potential side effects that may be experienced when losing weight loss. In regards to the ketogenic diet specifically, potential side effects that can occur in the first month of initiating the diet can include headache, irritability, low energy, constipation, lower blood pressure, and cravings for sweets and carbohydrates. Rare side effects include gallstones, gout, hair loss, or renal stones. There are also risks from blood draws including bleeding and

infection whenever skin surface is punctured. A total of 8 vials (4 vials at the start of study and 4 vials at the end of study) of blood will be collected in the study (estimated 48-60ml).

- Psychological assessment can cause some anxiety. This is minimized by the use of skilled and experienced assessors and the availability of the PI to see the participant who may be unduly disturbed by assessment. If acute psychopathology, e.g. suicidal depression, is observed during assessment or during treatment, appropriate referral for treatment will be made after consultation with the PD.
- Aside from these, there are no additional risks to physical well-being incurred through participation in the study. However, if at any point in the study you requires medical attention beyond the study team's capacity, consultation with the your physician will take place upon written consent. Furthermore, prior to entering the study, you will undergo a brief medical screening performed by the PD, part of the purpose of which will be to screen for the presence of unstable medical conditions (chest pain, cardiovascular disease, history of kidney stones).

POTENTIAL BENEFITS

Potential benefits include clinical improvement in terms of improvement in mood, cognition, quality of life, weight/adiposity, inflammation and lower risk for cardiovascular disease. Schizophrenia and Bipolar disorder, as discussed, are serious mental illnesses accompanied by adverse physical, psychological, and social/interpersonal costs. If this treatment can result in improvement in metabolic or mental health, it may lead to a larger study to confirm these results in a randomized trial.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

The alternative courses of treatment are available within the surrounding community and you will be educated about these alternative treatments. Alternative treatments for obesity and metabolic syndrome include medications, diet, and exercise. No standard treatments are being withheld. If you have been receiving these treatments, you will be allowed to continue them as long as they have been stable on these treatments for the past 3 months (See inclusions/exclusions). For example, participants taking weight loss/obesity

medications will not be excluded, however the study will require participants not to change the dose during the 4 month study. In other words, this treatment is for subjects who have tried (or are continuing to try) existing alternative treatments, yet remain symptomatic. Alternative treatments for psychiatric illness include medication management and psychotherapy. You will continue to see your psychiatrist for medication management of your illness. You will not be asked to limit your psychiatric medications or needed dosage changes. However, the medications used often have side effects including weight gain and insulin resistance. Part of the current study's rationale for investigating LCHF dietary intervention in these patients is to detect a signal for effectiveness in this special population on psychiatric medications that already have signs of insulin resistance or metabolic syndrome.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.
You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

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.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The purpose of this research study is to learn whether the LCHF diet is effective in improving metabolic and mental health in a cohort of outpatients with bipolar disorder or schizophrenia. Patient information may be provided to Federal and other regulatory agencies as required.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your

authorization for the research use or disclosure of your health information in this study, you must write to:
Dr. Shebani Sethi
401 Quarry Rd Ste 2206
MC 5723
Stanford, CA 94305

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to: name, telephone numbers, address, date of birth and age, electronic mail addresses, and Internet Protocol (IP) address numbers, medical record numbers, Current Weight, Health Information, Gender, Problem List, Psychiatric and Other Medical Diagnoses, Lab Test Results, History of Present Illness (HPI) Progress Notes, Medication Administration Record, and Current and Past Medications Prescribed.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Dr. Shebani Sethi
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff
- The Study Coordinator
- The Stanford University Bipolar Disorders Clinic
- The Stanford University INSPIRE Clinic

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on December 31, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____

Signature of Adult Participant Date

_____

Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment/Reimbursement
If you participate in this study, you will receive a $50 Amazon gift card at completion of the study.

Costs
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor
The Baszucki Brain Research Fund is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Shebani Sethi. You may contact her now or later at 650-721-4419.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Dr. Shebani Sethi at 650-721-4419.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at 650-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact Lauren Chang at 650-498-8459.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;

- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent