Full Protocol Title

Prebiotic Treatment in People with Schizophrenia

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Supported by:
The National Center for Complementary and Integrative Health

1 R61 AT009990-01

Study Intervention Provided by:

Jackson GI Medical

Tool Revision History

Version Number: 1.1
Version Date: 2/5/2019
Summary of Revisions Made: See attached “Summary of Review Responses” document.

Version Number: 1.2
Version Date: 3/26/2019
Summary of Revisions Made: See attached “Summary of Review Responses” document.

Version Number: 1.3
Version Date: 4/8/2019
Summary of Revisions Made: See attached “Summary of Review Responses” document.

Version Number: 1.4
Version Date: 6/13/2019
Summary of Revisions Made: See attached “Summary of Review Responses” document.

Version Number: 2.1
Version Date: 8/13/2019
Summary of Revisions Made: Per OHRP requirement, the “Potential Benefits” section of the consent document was revised to include a more detailed list of potential benefits to the participant.

Version Number 2.2
Version Date: 12/16/19
Summary of Revisions Made: Revised the BMI inclusion criterion to less than or equal to 40. Study medication name was changed from FOS to OEI due to manufacturer request; actual composition of the study medication was not changed.

Version Number 2.3
Version Date: 1/23/2020
Summary of Revisions Made: Samantha Trikeriotis, Joel Palachuvattil, and Sharon Pugh were added as study team members.

Version Number 2.4
Version Date: 7/16/2020
Summary of Revisions Made: Hanna Michel and Franklin Blatt were added, and Megan Powell removed from the study team roster.

Version 3
Version Date: 8/12/20
Summary of Revisions Made: Gopal Vyas was added, and Anne Werkheiser removed, from the study team roster. The PIS and PPSS acronyms on the Schedule of Evaluations were expanded to clarify the assessment names.

Version 4
Version Date: 9/17/20
Summary of Revisions Made: Heidi Wehring was removed from the study team roster; the Protocol Participation Status Sheet was removed from Days 1-9 on the Schedule of Evaluations; the adverse event section was revised to correct the inconsistencies in how we track and capture adverse events on the side effect checklist.

Version 5
Version Date: 1/26/21
Summary of Revisions Made: Administrative change - Clarification of the intent of the exclusion of antibiotics for acute use and current infections and not medications for longer term use with antibiotic properties.

Version 6
Version Date: 9/13/2022
Summary of Revisions Made: Administrative changes – Revisions to the study team roster: Added Colin Frazier; Removed Hanna Michel, Samantha Trikeriotis, and Samuel Kane-Gerard.

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PRÉCIS

Study Title

Prebiotic Treatment in People with Schizophrenia

Objectives

The primary objective of the study is to examine the effect of a 10-day course of the prebiotic: Prebiotin, an oligofructose-enriched inulin (OEI), on serum butyrate levels. We hypothesize that OEI, compared to placebo, will produce a greater increase in serum butyrate levels secondary to the stimulatory effects of OEI on the activity of known butyrate-producing bacteria.

Design and Outcomes

We will conduct a 10-day, double-blind, placebo-controlled, randomized clinical trial to examine the effect of OEI on serum butyrate levels. There will be two study phases: 1) a 2-week Evaluation Phase, during which potential participants will undergo baseline medical, vital sign, and symptom assessments to determine whether they meet inclusion criteria; and 2) a 10-day Double-blind Treatment Phase.

Participants who complete the 2-week Evaluation Phase and continue to fulfill inclusion criteria will be entered into the 10-day double-blind treatment phase. Participants will be randomly assigned to OEI or placebo-OEI, with approximately 10 participants in each group. Participants randomized to OEI will receive 4 grams of OEI, mixed in water, three times a day for 10 days, for a total dose of 12 grams. Participants randomized to placebo-OEI will receive 4 grams of maltodextrin, mixed in water, three times a day for 10 days. A non-blind pharmacist will dispense all study medications. The blind will be broken only if a medical emergency requires this information.

We will consent and evaluate up to 30 participants to reach the goal of approximately 24 participants randomized and 20 study completers. We will plan to randomize approximately 24 participants, because we anticipate a 10-20% attrition rate. We will consent and evaluate up to 30 participants, because we anticipate that some participants, who provide informed consent, may not meet eligibility criteria. However, we do not expect to need to consent 30 participants, because potential participants will be prescreened, through our partial HIPPA waiver, and those with obvious exclusion criteria (e.g. do not meet the age range criterion) will not undergo the informed consent process.

If a participant is unable to tolerate the study medication, then they will be withdrawn from study treatment, but we will continue to make every effort to collect scheduled study assessments.

All participants will receive the identical, standardized diet, provided by a registered dietician, which will consist of 3 meals and one snack. The daily diet breakdown is approximately 2700 calories with the following composition: 100 g protein, 400 g carbohydrates, 28 g fiber, 6.7% saturated fat, 28% total fat, 240 mg cholesterol and 4.4 g sodium.

Interventions and Duration

We are using a prebiotic, natural product: Orafti® Synergy1, sold in the US under the brand name Prebiotin®, for the study. Prebiotin® is an oligofructose-enriched inulin (OEI). Prebiotin® will be provided by Jackson GI Medical. Prebiotin® is considered a food powder, not a bacterial strain. Prebiotin® is a combination of chicory inulin fractions with selected chain lengths; the shorter chain inulin (oligofructose) is combined with longer chain inulin in essentially equal amounts. Inulins are indigestible polysaccharides and have been generally recognized as safe by the US Food and Drug Administration. Inulin consists of oligo- and polysaccharides composed of fructose units linked together by ß-(2, 1)-linkages. Almost every fructose chain is terminated by a glucose unit. The number of fructose and glucose units in inulin (Degree of Polymerization; DP) ranges between 2 and 60. Shorter chain inulin (oligofructose) consists of oligosaccharides obtained by partial enzymatic hydrolysis from inulin. Part of shorter chain inulin is terminated by a glucose unit. The degree of polymerization is less than 10. Longer chain inulin consists of inulin of which shorter fractions were removed. Almost every molecule is terminated by a glucose unit and has a DP of 10 or higher.

Prebiotin® is a fine, white to slightly yellow powder, which is hygroscopic and slightly sweet. The product is produced by Beneo-Orafti SA and distributed in the US by Jackson GI Medical.

Prebiotin® meets full GMP requirements of characterization and standardization and full requirements contained in the NCCIH policy for Natural Product Ingredients (see https://nccih.nih.gov/research/policies/naturalproduct.htm#ctconsiderations). The product specification sheet includes the taxonomic nomenclature and the analysis of the product for contaminants/impurities, including microorganisms. This specification sheet also contains solubility information and minimum durability/stability information. Each parameter contains the limit, the units, the reference method and the frequency of continued testing. In addition, the information for nutritional declaration in the US by 21 CFR 101.9 is included in the specification sheet.

The total length of study participation for each individual participant will be 25 days. There will be 5 study visits: 2 visits during the 2-week Evaluation Phase and 3 visits during the Double-blind Treatment Phase.

The total time of study participation is 18-20 hours. The two Evaluation Phase visits will take a combined total of 3-5 hours to complete. The Day 0 and Day 11 visits will take approximately 7 hours each to complete; on these days participants will undergo the inulin (OEI) challenge to assess the extent to which OEI has modified the biological signature: serum butyrate levels. The extended length of the visit is due to the need to wait 6 hours for the peak in serum butyrate following the inulin administration. The Day 10 visit will take approximately 1 hour to complete.

Sample Size and Population

Participants (n=20) will be of either sex and any race, and between 18-60 years old. Participants will be recruited from the greater Baltimore metropolitan area. They will meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (APA, 2013) criteria for schizophrenia or schizophreniform or schizoaffective disorder. A best estimate diagnostic approach will be utilized in which information from the Structured Clinical Interview for DSM-5 (First et al, 2015) is supplemented by information from family informants, previous psychiatrists, and medical records to generate a diagnosis. Participants will be judged by their primary clinician to be clinically stable and will be prescribed the same antipsychotic and dose for at least 14 days prior to study entry. In light of the potential impact of obesity on the gut microbiota (Brahe et al, 2013), participants will be required to have a body mass index (BMI) ≤ 40, i.e., we will restrict the population to those with normal or mild to moderate increased BMI and exclude potential participants who are morbidly obese. The proposed BMI criterion reflects the typical range of BMI values of people with schizophrenia who enter our treatment units and studies, and will serve to minimize the impact of morbid obesity on the study results. We will not restrict the type of antipsychotic, with which the participant is treated.

Participants with inflammatory bowel diseases or other gastrointestinal disorders, whose pathology or treatment could significantly increase the risk associated with the proposed treatment; who have an organic brain disorder; who have an intellectual disability; who have been treated with an antibiotic or immune therapy within the last three months; who have been treated with a prebiotic or probiotic within the last three months; who are unable to understand English or cooperate with study procedures; or who meet DSM-5 criteria for alcohol or substance use disorders (except Tobacco Use Disorder) within the last 3 months will be excluded. Female participants who are pregnant or lactating will be excluded. Participants must be judged competent to participate in the informed consent process and provide voluntary informed consent.

The use of the proposed inclusion/exclusion criteria will result in a study population, which is representative of hospitalized people with schizophrenia and related disorders; minimizes the effect of potential confounder variables; and maximizes the safety of the study protocol.

The study biostatistician will use a permuted block randomization system (block sizes 2 or 4), in which treatment assignment order is random within each block, with an equal number of participants assigned to each treatment, to generate a list of treatment assignments. Thus, it will be difficult to ascertain the next treatment assignment, even if a participant becomes unblinded, while any imbalance in the number of participants between the treatment groups will be kept within tight limits. All raters, investigators and other staff will be blind to treatment assignment except for the pharmacist. The pharmacist does not participate in assessing any of the primary symptom or side effect dependent variables and conveys no information about treatment assignment to participants or staff except in a medical emergency.

1. STUDY OBJECTIVES

1.1 Primary Objective

In the context of a 10-day, double-blind, placebo-controlled, randomized clinical trial (RCT), we will examine whether the prebiotic: Prebiotin (12g/day), an oligofructose-enriched inulin (OEI), increases serum butyrate levels. Participants with schizophrenia or a related disorder will be randomly assigned to OEI or placebo-OEI, with approximately 10 participants in each group. We hypothesize that OEI, compared to placebo, will produce a greater increase in serum butyrate levels secondary to the stimulatory effects of OEI on known butyrate-producing bacteria.

1.2 Secondary Objectives

N/A

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

People with schizophrenia have a broad range of neurocognitive impairments, including abnormalities in attention, executive function, verbal and visual learning and memory, working memory, processing speed, and social cognition (Nuechterlein et al, 2004). These impairments are major determinants of functional outcome in schizophrenia (Green, 1996; Green et al, 2004). Unfortunately, first and second generation antipsychotics have limited benefits for these impairments (Keefe et al, 2007; Buchanan et al, 2007), which has led to the evaluation of add-on pharmacological agents for the treatment of cognitive impairments, but results, to date, have been largely disappointing (Choi et al, 2013; Buchanan et al, 2007; Freedman et al, 2008; Winterer et al, 2008; Lieberman et al, 2013; Umbricht et al, 2014). Cognitive remediation and other non-pharmacological strategies have shown some promise, but the observed beneficial effects rarely generalize beyond the measures included in the training exercises (Dixon et al, 2010). In the absence of an effective treatment, cognitive impairments remain a critical unmet therapeutic

need, and the development of a novel approach for the treatment of these impairments remains a central therapeutic challenge.

2.2 Study Rationale

Over the past 10 years, considerable evidence has emerged from animal studies to suggest that the gut microbiome has significant effects on brain development and behavior, with bidirectional communication between the enteric nervous system, gut and the central nervous system (CNS) (Diaz Heijtz et al, 2011; Douglas-Escobar et al, 2013; Dinan et al, 2014). The gut microbiota have been shown to: a) produce multiple neurotransmitters, including gamma-aminobutyric acid (GABA), dopamine, norepinepherine, and serotonin, and may regulate CNS levels of these neurotransmitters; b) modulate brain development through the regulation of synaptogenesis; and c) modulate the levels of stress hormones during brain development, which may affect stress response and anxiety behavior (Diaz Heijtz et al, 2011; Dinan et al, 2014; Sudo et al, 2004; O'Mahony et al, 2015). Moreover, the gut microbiota effects the production of neurotrophins, including brain-derived neurotrophic factor (BDNF), which plays a significant role in neurogenesis and synaptic plasticity (Sudo et al, 2004; Nemani et al, 2015).

The gut microbiome may also affect brain development and function through its regulation of immune system function, which is mediated, in part, through the production of short-chain fatty acids (SCFA). There are three major SCFAs: butyrate, propionate, and acetate. Butyrate is of particular interest, since it plays a key role in maintaining gut homeostasis and epithelial integrity: butyrate is the primary energy source for intestinal colonocytes; and, of the three SCFAs, butyrate appears to have the most pronounced effects on immune system function and may exert its effects directly through immune pathways and indirectly through the maintenance of the integrity of the intestinal-blood barrier (Hamer et al, 2008; Louis et al, 2010; Brahe et al, 2013; Vital et al, 2014). The intestinal-blood barrier restricts the entrance of toxins, pathogens and antigens into the blood circulation; thus, increased permeability could lead to the entrance of substances and subsequent immune response.

The multiple effects of the gut microbiome on brain development and behavior, suggest that alterations in the gut microbiome may occur in schizophrenia and play a part in the pathophysiology of the disorder. The increased prevalence of gastrointestinal disorders in schizophrenia; the association of infections, including infections with Toxoplasma gondii, which can induce intestinal inflammation, with the risk for the development of schizophrenia; and evidence of increased gut permeability provide further indirect evidence for disruption of the gut microbiome in this disorder (Dinan et al, 2014; Nemani et al, 2015; Severance et al, 2012; Severance et al, 2014). Although a number of studies have been conducted in other neuropsychiatric disorders, including autism (Parracho et al, 2005; Tomova et al, 2015), which demonstrate altered bacterial composition of the gut microbiome, there is only one published study of the microbiome in schizophrenia. Yolken and colleagues examined the oropharyngeal microbiome in people with schizophrenia,

and found that there were increased levels of the bacteriophage, Lactobacillus phage phiadh, genome in the schizophrenia group, which were correlated with co-occurring immunological disorders (Yolken et al, 2015). There is one published study of gut microbiota in schizophrenia. Shen and colleagues found a significant reduction in butyrate producers in people with schizophrenia compared to healthy controls (Shen et al. Schiz Res, https://doi.org/10.1016/j.schres.2018.01.002).

The purpose of this study is to examine changes in serum butyrate levels with the prebiotic: Prebiotin (12g/day), an oligofructose-enriched inulin (OEI); the effect of OEI on the composition of the gastrointestinal microbiota in people with schizophrenia; and the relationship of the composition of the gut microbiota to various clinical, cognitive, and neuroimaging variables.

3. STUDY DESIGN

In a sample of inpatients with a DSM-IV-TR/DSM-5 diagnosis of schizophrenia or schizoaffective disorder, we will conduct a 10-day, double-blind, placebo-controlled, randomized clinical trial to examine the effect of a prebiotic, oligofructose-enriched inulin (OEI) on serum butyrate levels; the relative preponderance of butyrate-producing bacteria in the gut microbiome; and the relationship of these measures to cytokine or gut permeability measures, signs and symptoms of schizophrenia, and/or metabolic measures. We will consent and evaluate up to 30 participants to reach the goal of approximately 24 participants randomized and 20 study completers. We will plan to randomize approximately 24 participants, because we anticipate a 10-20% attrition rate. We will consent and evaluate up to 30 participants, because we anticipate that some participants, who provide informed consent, may not meet eligibility criteria. However, we do not expect to need to consent 30 participants, because potential participants will be prescreened, through our partial HIPPA waiver, and those with obvious exclusion criteria (e.g. do not meet the age range criterion) will not undergo the informed consent process. Participants will be randomized to either OEI, 12 g/day or matching placebo, with approximately 10 participants in each group. We will use an inpatient sample in order to standardize meals, exercise and environmental mediators. We will recruit patients from the Treatment Research Program inpatient unit, Maryland Psychiatric Research Center, University of Maryland School of Medicine.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

The overall goal of this project is to determine whether oligofructose-enriched inulin (OEI) is an effective treatment for schizophrenia. We will use an inpatient sample in order to standardize meals, exercise and environmental mediators. The population to be included will not include any people in prisons, but will include psychiatric inpatients who are court-ordered for care. The research on understanding the gut microbiota, as well as understanding if over the counter prebiotics may change the gut microbiota, have minimal inherent risk regardless of the court-ordered status of the research participants. This research, however, can only take place in a controlled living environment with all people receiving standardized meals and similar environmental influences to have unflawed

results. Court-ordered patients comprise the majority of the inpatient psychiatric unit population. The environment at Spring Grove Hospital Center is identical for both court-ordered and non-court-ordered patients on the Treatment Research Unit.

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study:

1) DSM-IV-TR /DSM-5 diagnosis of schizophrenia or schizoaffective disorder;
2) Age 18-60 years;
3) Considered clinically stable by the treating psychiatrist;
4) Currently treated with an antipsychotic, with no dose changes in last 14 days;
5) Ability to participate in the informed consent process, as determined by a score of 10 or greater on the Evaluation to Sign Consent;
6) BMI ≤ 40

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation:

1) Gastrointestinal disorders, including, but not limited to Crohn's Disease, Irritable Bowel Syndrome, Celiac Disease, whose pathology or treatment could alter the presentation or treatment of schizophrenia or significantly increase the risk associated with the proposed treatment protocol
2) Organic brain disorder, including cerebrovascular accident; epilepsy; traumatic brain injury, Loss of consciousness (LOC) for more than 30 minutes
3) Intellectual disability
4) Acute antibiotic use
5) Immune therapy within the last three months
6) Prebiotic or probiotic treatment within the last three months
7) Inability to understand English
8) Inability to cooperate with study procedures
9) Pregnant or lactation secondary to pregnancy
10) Meet DSM-5 criteria for alcohol or substance use disorders (except Tobacco Use Disorder) within last 3 months

4.3 Study Enrollment Procedures

Potential participants will be recruited from the MPRC Treatment Research Program, and will consist of people who are currently hospitalized on the TRP or who are admitted to the TRP over the course of the study. We chose to limit the study population to inpatients, so we could standardize the diet across participants in this phase of the project. Reasons for ineligibility or non-participation of eligible candidates will be documented in the Enrollment Log.

The consent form will include an explanation of the risks and benefits of participation; assurances of confidentiality; and an explanation that participation is entirely voluntary, the decision to participate will in no way influence or restrict services at participating sites, and the participant is free to withdraw at any time without negative consequences. As some potential participants will have poor reading skills, the consent form will be read aloud to all participants in tandem with their own silent reading of the document. The individual securing consent will review any points about which the participant is unclear, and the participant will be invited to ask questions as needed. Our research staff is carefully trained in strategies for interacting with people with severe mental illness, including speaking slowly and clearly, stopping to summarize frequently, and providing time for questions. They are all supervised by senior staff members. All participants who express willingness to provide consent will be queried about the consent form in order to ensure that they have adequate understanding of the study requirements. This questioning is performed systematically, and research staff members document that this review has been completed. After reading the consent, and before obtaining a signature, a brief questionnaire is administered to verify that the participant is competent to provide consent and has demonstrated comprehension of the consent document. This questionnaire is attached to the informed consent form and is completed immediately after explaining the informed consent form and before obtaining the participant's signature on the form. If the participant does not understand the consent form, the recruiter will try to explain points of confusion, and administer the questionnaire again. Those failing to answer the questions adequately will not be recruited into the study. The recruiter will also make a clinical judgment and not recruit participants who appear unable to grasp key aspects of the procedure. This approach, which requires a proactive demonstration on the part of the participant that they understand what is being requested, has been used extensively by investigators at the MPRC. Included participants must also be judged competent to consent by the Evaluation to Sign Consent (ESC) questionnaire (DeRenzo et al 1998). Per University of Maryland School of Medicine IRB regulations, a copy of the signed consent form is given to the participant, a copy is placed in the person's medical record, and the original is kept by the PI.

Research assistants obtaining informed consent will be experienced clinicians. They will receive detailed and standardized training as to how to obtain informed consent from people with serious mental illnesses. They will be observed obtaining informed consent from a study participant by senior staff prior to being allowed to enroll participants on their own.

The study biostatistician will use a permuted block randomization system (block sizes 2 or 4), in which treatment assignment order is random within each block, with an equal number of participants assigned to each treatment, to generate a list of treatment assignments. Thus, it will be difficult to ascertain the next treatment assignment, even if a participant becomes unblinded, while any imbalance in the number of participants between the treatment groups will be kept within tight limits. All raters, investigators and other staff will be blind to treatment assignment except

for the pharmacist. The pharmacist does not participate in the assessment of any of the primary symptom or side effect dependent variables and conveys no information about treatment assignment to participants or staff except in a medical emergency.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Participants who continue to fulfill inclusion criteria will enter the 10-day double-blind treatment phase. Participants will be randomly assigned to OEI or placebo-OEI, with approximately 10 participants in each group. Participants randomized to OEI will receive 4 grams of OEI, mixed in water, three times a day for 10 days. We chose the 12 grams/day dose, because a previous study suggests that this dose is well tolerated and based on data from a pilot study conducted by our co-investigators. Participants randomized to placebo will receive maltodextrin (4 grams), mixed in water, three times a day for 10 days. Maltodextrin is a polysaccharide composed of glucose units, a mixture of chains that vary from 3 to 17 glucose units long; and is freely soluble or readily dispersible in water and is a quickly digested carbohydrate. Maltodextrin has previously been used in studies evaluating the effect of OEI prebiotics (Abrams et al, 2005; Casellas et al, 2007; Roller et al, 2007; De Peter et al, 2008; Dehghan et al, 2014), and produces minimal changes in inflammatory and metabolic measures (Casellas et al, 2007; Dehghan et al, 2014).

5.2 Handling of Study Interventions

The OEI will be provided in bulk by Jackson GI Medical in the form of Prebiotin. OEI is considered a food supplement and is being used for its indication to improve gut bacteria composition, thus it is not a drug product nor is it being used for any other indication. Maltodextrin and OEI have a similar appearance when dissolved in water and both have a slightly sweet taste, which will help to preserve the blind. A non-blind pharmacist will dispense all study medications. The blind will be broken only if a medical emergency requires this information.
In order to monitor compliance, participants will be observed by research staff while they ingest the study medication. Since all participants will be inpatients, we do not expect problems with compliance, but we will carefully monitor compliance patterns, which will be described within each treatment group as part of any presentation of study results.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants may continue taking their prescribed antipsychotic, with no dose changes in the 14 days prior to signing consent.

5.3.2 Required Interventions

N/A

5.3.3 Prohibited Interventions

Participants may not have been taking antibiotic or immune therapy, or prebiotic or probiotic treatment within the last three months prior to signing consent.

5.4 Adherence Assessment

We will strive to ensure that all participants receive ≥ 90% of their assigned medication. The 90% criterion increases the likelihood that participants will receive adequate treatment to evaluate the effect of OEI on the biological signature. In order to monitor adherence, participants will be observed by research staff while they ingest the study medication. Since all participants will be inpatients, we do not expect problems with adherence, but we will carefully monitor adherence patterns, which will be described within each treatment group as part of any presentation of study results.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Schedule of Events	2-Week Evaluation Phase	Baseline, Enrollment, Randomization		Double-Blind Treatment Phase		
Encounter # →	P1V1	P2V0	P2V1		P2V2	P2V3
Day of Study →	Day -14 to -1	Day -1	Day 0	Day 1-9	Day 10	Day 11
Procedure ↓						
Informed consent and ESC	X					
Eligibility Documentation	X					
Protocol Initiation Sheet	X					
Recommendation for Inclusion Form	X					
Brief Psychotropic Medications Form	X					X
Brief Non-Psychotropic Medications Form	X					X
Demographic Forms	X					
Fagerstrom, short version	X					
SCID-Interview*	X					

Medical History and EKG**	X					
Physical Exam and height**	X					
Diet Log	X					
CMP-14, CBC Lipid Panel	X					X
UA; Urine Pregnancy Test (females)	X					X
Side Effect Checklist			X		X	
BPRS			X			X
HAM-A			X			X
Cytokines, C-reactive protein			X			X
ASCA and AGA IgG			X			X
Tryptophan, Kynurenine, KYNA & 3-HK			X			X
OEI Challenge			X			X
Serum Butyrate: pre-prandial, 2 hr and 6 hr after OEI challenge			X			X
OEI or Placebo (Day1-10)				X	X	
Fully Digestible Meal		X			X	
Stool Sample Collection		X			X	
Vital Signs, including weight, BP and pulse	X	X	X		X	X
Protocol Participation Status Sheet	X	X	X		X	X

*SCID interview results may be used, if completed within the past 5 years. The Drug Misuse section still needs to re-done at time of visit.

**Medical history, EKG, physical exam, height and other screening and baseline measures can be collected from the TRP admission assessment if completed within the past 2 months.

6.2 Description of Evaluations

Once participants sign the informed consent form, they will enter a 2-week Evaluation Phase (Screening and Baseline), during which they will undergo baseline medical, vital sign, and symptom assessments to determine whether they meet inclusion criteria. This will include a comprehensive medical history and physical examination. We will obtain baseline CBC, Chemistry-14 Panel, lipid panel and urinalysis assessments. Weight, height and vital signs (i.e., heart rate, pulse, blood pressure) will be assessed weekly throughout the study. The diagnosis of schizophrenia or related disorder will be confirmed by a structured psychiatric examination, the Structured Clinical Interview for DSM-5. Participants will also have baseline symptom assessments completed. Participants continuing into the Double-blind Treatment phase will repeat baseline symptom assessments during week 2. All participants will receive the identical, standardized diet, provided by a registered dietician, which will consist of 3 meals and one or two snacks. The daily diet breakdown is approximately 2700 calories with the following composition: 100 g protein, 400 g carbohydrates, 28 g fiber, 6.7% saturated fat, 28% total fat, 240 mg cholesterol and 4.4 g sodium.

Participants who continue to fulfill inclusion criteria will enter the 10-day double-blind treatment phase. Participants will be randomly assigned to OEI or placebo-OEI, with approximately 10 participants in each group. The OEI will be provided by Jackson GI Medical in the form of Prebiotin. OEI is considered a food supplement and is being used for its indication to improve gut bacteria composition, thus it is not a drug product nor is it being used for any other indication. Participants randomized to OEI will receive 4 grams of OEI, mixed in water, three times a day for 10 days. We chose the 12 grams/day dose, because a previous study suggests that this dose is well tolerated and based on data from a pilot study conducted by our co-investigators. Participants randomized to placebo will receive maltodextrin (4 grams), mixed in water, three times a day for 10 days. Maltodextrin is a polysaccharide composed of glucose units, a mixture of chains that vary from 3 to 17 glucose units long; and is freely soluble or readily dispersible in water and is a quickly digested carbohydrate. Maltodextrin has previously been used in studies evaluating the effect of OEI prebiotics (Abrams et al, 2005; Casellas et al, 2007; Roller et al, 2007; De Peter et al, 2008; Dehghan et al, 2014), and produces minimal changes in inflammatory and metabolic measures (Casellas et al, 2007; Dehghan et al, 2014). Maltodextrin and OEI have a similar appearance when dissolved in water and both have a slightly sweet taste, which will help to preserve the blind. A non-blind pharmacist will dispense all study medications. The blind will be broken only if a medical emergency requires this information. If this occurs, the participant will be withdrawn from the study.

In order to evaluate the impact of OEI treatment, we will examine change in serum butyrate levels following treatment. There will be two test days: a) baseline (Day 0), prior to randomization to OEI or placebo; and b) Day 11, following the 10 day course of OEI/placebo treatment. We will use OEI for the inulin challenge. On the night prior to each test day, participants will receive a completely digestable and non-fermentable meal, e.g. lasagna and up to two fully digestable snacks (e.g.

chips). They will then fast from midnight until the morning, when they will receive their standard, low-fiber breakfast and OEI, 12g. We will collect fasting, 2 hour and 6-hour blood samples from each participant. Participants will be able to receive a light digestable meal 4 hours after OEI administration. The Day 11 change in serum butyrate levels following the OEI challenge dose (2 or 6-hour minus fasting morning serum butyrate level) will be compared to the Day 0 change in serum butyrate levels to determine whether the 10-day OEI treatment regimen modified the hypothesized biological signature through increased activity of butyrate-producing bacteria. Serum butyrate will be quantified by LC-MS/MS, conducted by the School of Pharmacy Mass Spectrometry Center.

6.2.1 Screening Evaluation

Consenting Procedure

Before any screening procedure is performed, informed consent must be obtained. There will be a single informed consent form that describes both the screening and study procedures.

Research assistants obtaining informed consent will be experienced clinicians. They will receive detailed and standardized training as to how to obtain informed consent from people with serious mental illnesses. They will be observed obtaining informed consent from a study participant by senior staff prior to being allowed to enroll participants on their own.

The consent form will include an explanation of the risks and benefits of participation; assurances of confidentiality; and an explanation that participation is entirely voluntary, the decision to participate will in no way influence or restrict services at participating sites, and the participant is free to withdraw at any time without negative consequences. As some potential participants will have poor reading skills, the consent form will be read aloud to all participants in tandem with their own silent reading of the document. The individual securing consent will review any points about which the participant is unclear, and the participant will be invited to ask questions as needed. Our research staff is carefully trained in strategies for interacting with people with severe mental illness, including speaking slowly and clearly, stopping to summarize frequently, and providing time for questions. They are all supervised by senior staff members. All participants who express willingness to provide consent will be queried about the consent form in order to ensure that they have adequate understanding of the study requirements. This questioning is performed systematically, and research staff members document that this review has been completed. After reading the consent, and before obtaining a signature, a brief questionnaire is administered to verify that the participant is competent to provide consent and has demonstrated comprehension of the consent document. This questionnaire is attached to the informed consent form and is completed immediately after explaining the informed consent form and before obtaining the participant's signature on the form. If the participant does not understand the consent form, the recruiter will try to explain points of confusion, and administer the questionnaire again. Those failing to answer the questions

adequately will not be recruited into the study. The recruiter will also make a clinical judgment and not recruit participants who appear unable to grasp key aspects of the procedure. This approach, which requires a proactive demonstration on the part of the participant that they understand what is being requested, has been used extensively by investigators at the MPRC. Included participants must also be judged competent to consent by the Evaluation to Sign Consent (ESC) questionnaire (DeRenzo et al 1998). Per University of Maryland School of Medicine IRB regulations, a copy of the signed consent form is given to the participant, a copy is placed in the person's medical record, and the original is kept by the PI. Consent for each participant will be documented on the Documentation of Consent (DOC) form.

Screening

Once participants sign informed consent they will enter a 2-week Evaluation Phase (P1V1, Days -14 to -1)), during which they will undergo baseline medical, vital sign, and symptom assessments to determine whether they meet inclusion criteria. Psychiatric, Medical history, EKG, physical exam, height and other screening and baseline measures can be collected from the TRP admission assessment if completed within the past 2 months.

This will include:

- Demographic information: Documentation of age eligibility
- SCID-Interview: The diagnosis of schizophrenia from the medical record will be confirmed by a structured psychiatric examination, the Structured Clinical Interview for DSM-5. The SCID interview can be re-used if completed within the past 5 years, with the Drug Misuse section re-completed at time of visit.
- Medical and safety assessments to rule out excluded medical conditions and determine any clinically significant abnormal laboratory values:
    - Medical history
    - Physical examination
    - Electrocardiogram (EKG)
    - CBC
    - Fasting chemistry panel
    - Lipid panel
    - Urinalysis assessments including a pregnancy test for females
    - Vital signs: Blood pressure, heart and respiratory rates, height and weight, prior to randomization to the intervention; weight and height measurements will be used to calculate BMI, which must be less than ≤ 40 for eligibility.
- Dietary assessment: We will review the diet of each participant for up to a week prior to their study entry.
- Smoking form: Document smoking status of participants.

- Recommendation for Inclusion Form: Documents clinical stability, absence of a history of intellectual disability, and ability to cooperate with study procedures.
- Psychotropic and non-psychotropic concomitant medication forms: We will document all current medications including dosage, date started, and route of administration.
- Stool Sample: Participants will provide a baseline stool sample prior to the initiation of study medication.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment is defined as the randomization date, which will be recorded on a case report form and entered into the study database. The allowable window between screening and randomization is 14 days.

Baseline Assessments

For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments are performed against which to measure the study outcome (P2/V1, Day 0). Participants who continue to fulfill inclusion criteria will enter the 10-day double-blind treatment phase. Participants will be randomly assigned to OEI or placebo-OEI, with approximately 10 participants in each group.

- OEI Challenge: On the night prior to each test day, participants will receive a completely digestible and non-fermentable meal, e.g. lasagna. They will then fast from midnight until the morning, when they will receive their standard breakfast and OEI, 12g.
- Serum Butyrate: In order to evaluate the impact of OEI treatment, we will examine change in serum butyrate levels following treatment. We will collect baseline, 2-hour and 6-hour blood samples from each participant. The blood samples will be analyzed at the University of Maryland School of Pharmacy Mass Spectrometry Center.
- The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962): the BPRS total score will be used to measure global psychopathology. The four BPRS positive symptom items - conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content - will be used to measure positive psychotic symptoms.
- Hamilton Anxiety Rating Scale (HAM-A; Seedat et al, 2007): The HAM-A will be used to measure symptoms of anxiety.
- Peripheral Cytokines and Other Laboratory Measures: Serum cytokines; highly sensitive C-reactive protein (CRP); and adiponectin and leptin. Serum cytokines will be measured by the Cytokine Core Laboratory at the University of Maryland using Luminex® 100 Multianalyte System or ELISA at baseline and endpoint or the Immune Lab at Johns Hopkins. The primary cytokines to be analyzed initially will be IL-1β, IL-6, and TNF-α, and the acute phase protein C-reactive protein (CRP), which is induced by increased

cytokine levels, including IL-6. The other cytokines listed will be initially stored and analyzed at a later date.

- ASCA and AGA IgG: We will use Anti-Saccharomyces Cerevisiae Antibodies (ASCA) to measure the integrity of the gut-blood barrier. ASCA are antibodies that develop against antigens presented by the cell wall of the yeast, Saccharomyces cerevisiae. ASCA are elevated in people with intestinal inflammation (e.g. Crohn's Disease) and increased intestinal permeability (Rutgeerts and Vermeire, 1998; Makharia et al, 2007), which supports their use as a marker of increased intestinal permeability (Irvine et al, 2000; Barta et al, 2003). AGA IgG antibodies have been found to be present in about 1/3 people with schizophrenia and linked to diseases such as celiac disease and gluten sensitivity and are known to modulate gut bacteria and potentially butyrate. ASCA IgA and IgG will be measured, using the protocol of the commercially available ELISA kit (Orgentec, Mainz, Germany). We will collect ASCA levels at baseline and the end of week 10. We will also measure Antigliadin Antibodies (AGA IgG). The blood samples will be analyzed at the University of Maryland School of Pharmacy Mass Spectrometry Center.
- Vital Signs: Blood pressure, heart and respiratory rates, height and weight, prior to randomization to the intervention; weight and height measurements will be used to calculate BMI.
- Side Effect Checklist (SEC): The SEC will be used to assess the baseline presence of potential side effects.

Randomization

The study biostatistician will use a permuted block randomization system (block sizes 2 or 4), in which treatment assignment order is random within each block, with an equal number of participants assigned to each treatment, to generate a list of treatment assignments. Thus, it will be difficult to ascertain the next treatment assignment, even if a participant becomes unblinded, while any imbalance in the number of participants between the treatment groups will be kept within tight limits.

6.2.3 Blinding

All study clinical, laboratory, medical and safety assessments will be done by research assistants, who are blind to treatment assignment. The study biostatistician will be blinded until the final lock of the database. The P.I. and the co-investigators will be blinded until all study analyses have been completed.

Only the research pharmacist will be unblinded. The research pharmacist will be responsible for requesting the treatment assignment from the study biostatistician, who will use a permuted block randomization system (block sizes 2 or 4), in which treatment assignment order is random within each block, with an equal number of participants assigned to each treatment, to generate a list of treatment assignments. The research pharmacist will be responsible for preparing the study interventions based on the treatment assignment he receives from the biostatistician. Maltodextrin and OEI have a similar appearance when dissolved in water and both have a slightly sweet taste, which will help to preserve the blind.

The study biostatistician will have no access to the data, nor will he have any influence on the conduct of any of the outcome assessments.

The blind will be broken only if a medical emergency requires this information. The data analyst will be blinded to treatment assignment and will prepare any requested blinded reports for the Data Safety Monitoring Board (DSMB) . If the DSMB requests unblinded study reports, then the data analyst will work with the DSMB to prepare these reports (see attached DSMB roster: Appendix III).

6.2.4 Double-Blind Treatment Phase

Study visits must be performed on the weeks indicated in the Schedule of Evaluations.

- Days 1-9:
  - OEI or Placebo
  - Stool Sample (after Day 5)
- Day 10 (P2V2):
  - OEI or Placebo
  - Vital signs
  - SEC

6.2.5 Completion/Final Evaluation

- Day 11 (P2V3):
  - OEI Challenge
  - CBC
  - Fasting chemistry panel
  - Lipid panel
  - Urinalysis assessments including a pregnancy test for females
  - BPRS
  - HAM-A
  - Peripheral cytokines and other laboratory measures (C-reactive protein, Tryptophan, Kynurenine, KYNA, and 3-HK)
  - ASCA and AGA IgG
  - Serum butyrate
  - Vital signs
  - Psychotropic and non-psychotropic concomitant medications

The DSMB or IRB will conduct a safety review of AE's and SAE's, which will yield a decision to cease enrollment for the study. Participants may also request to be withdrawn from the study at any time. Once a participant is discontinued from the

study for whatever reason, completion ratings will be performed if possible. This includes all laboratory tests and rating scales below. The study team will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation, or until the resolution or stabilization of an event. At each study visit, the study team will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7. SAFETY ASSESSMENTS

Participant safety will be monitored once an individual is enrolled in the study. The study medication, OEI in the form of Prebiotin, may be associated with adverse effects. The most common side effects are flatulence, bloating, and abdominal discomfort. We will make every attempt to minimize all study-related risks. We will carefully monitor patients and psychiatric symptoms throughout the study. All patients are in the inpatient setting with 24 monitoring and care.

7.1 Specification of Safety Parameters

All participants will receive a complete medical history and physical examination, including vital signs: blood pressure, heart and respiratory rates, height and weight, prior to randomization to the intervention; weight and height measurements will be used to calculate BMI. We will collect baseline EKG and baseline and end of studyCBC; complete metabolic panel (CMP), including BUN/Creatinine, electrolytes, glucose, LFTs, and lipid panel; and U/A assessments. The CMP will be collected after fasting for at least 8 hours. Female participants of child-bearing potential will have a pregnancy test at baseline and Day 11.

The Side Effect Checklist (SEC) is designed to assess medication side effects commonly associated with pharmacological treatments. In addition, if not already assessed, the SEC is modified for the purpose of the assessment of specific side effects associated with the particular intervention under study; in this case OEI. The SEC version to be used in the proposed study rates 35 potential side effects, and comprehensively covers the side effects that have been previously reported with OEI, i.e., bloating, flatulence, and abdominal pain. In addition, there are three “other” spaces for idiosyncratic participant complaints, which are not usually associated with medication treatment. The SEC will be conducted at baseline and Day 10.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

OEI is considered a food supplement and is being used for its indication to improve gut bacteria composition, thus it is not a drug product nor is it being used for any other indication. Participants randomized to OEI will receive 4 grams of OEI, mixed in water, three times a day for 10 days. We chose the 12 grams/day dose, because a previous study suggests that this dose is well tolerated and based on data from a pilot study conducted by our co-investigators.

Participants randomized to placebo will receive maltodextrin (4 grams), mixed in water, three times a day for 10 days. Maltodextrin is a polysaccharide composed of glucose units, a mixture of chains that vary from 3 to 17 glucose units long; and is freely soluble or readily dispersible in water and is a quickly digested carbohydrate. Maltodextrin has previously been used in studies evaluating the effect of OEI prebiotics (Abrams et al, 2005; Casellas et al, 2007; Roller et al, 2007; De Peter et al, 2008; Dehghan et al, 2014), and produces minimal changes in inflammatory and metabolic measures (Casellas et al, 2007; Dehghan et al, 2014).

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is any untoward medical occurrence in a participant during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study. Adverse events are to be recording regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is one that meets one or more of the following criteria:

- Results in death.
- Results in persistent or significant disability/incapacity.
- Results in or prolongs an existing inpatient hospitalization (even if the hospitalization is a precautionary measure for observation).
- Is a congenital anomaly/birth defect in offspring of subjects taking the product regardless of time to diagnosis.
- Is cancer.
- Is the result of an overdose, whether accidental or intentional.
- Is a suicide attempt (not suicidal ideation only).

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation, or until the resolution or stabilization of an event. At each study visit, the study team will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Laboratory assessments that we will collect are EKG; CBC; complete metabolic panel (CMP), including BUN/Creatinine, electrolytes, glucose, LFTs, and lipid panel; and U/A assessments. Female participants of child-bearing potential will have a pregnancy test. Clinically significant abnormal laboratory values are defined as any values outside the reference range for a laboratory.

The Side Effect Checklist (SEC) is designed to assess medication side effects commonly associated with pharmacological treatments. In addition, if not already assessed, the SEC is modified for the purpose of the assessment of specific side effects associated with the particular intervention under study; in this case OEI. The SEC version to be used in the proposed study rates 35 potential side effects, and comprehensively covers the side effects that have been previously reported with OEI, i.e., bloating, flatulence, and abdominal pain. In addition, there are three "other" spaces for idiosyncratic participant complaints, which are not usually associated with medication treatment. The SEC rates each side effect on a 4-point scale (1: none to 4: severe). The SEC will be conducted at baseline and Day 10.

The following definitions will be used to define an adverse event:

- Any SEC item for which there is a two-point increase over the baseline assessment of the item; and
- Any SEC item that is rated "4" at Day 10, but was not rated "4" in the baseline assessment.

7.4 Reporting Procedures

The Study PI and Independent Monitoring Committee will be responsible for determining whether an AE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

The following scale will be used to grade adverse events when reporting to the Data Safety Monitoring Board. This scale is used when reporting all adverse events, including side effects assessed with the SEC:

1. Mild: no intervention required; no impact on activities of daily living (ADL) (SEC item score=2)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL (SEC item score=3)
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL (SEC item score=4)

Serious adverse events will be reported to the DSMB, the UMB IRB, and NCCIH by the Principal Investigator (P.I.) or their designated POC in accordance with requirements.

- All serious AEs will be reported to the NCCIH Program Officer, the DSMB, and the UMB IRB within 3 business days of the investigator becoming aware of the event. Any follow-up reports are to be submitted as new information regarding the event becomes available. Adverse events that are determined to be unexpected and probably related to study procedures, regardless of severity, will be reported to NCCIH and the UMB IRB within 5 business days. These AEs will be reported to the DSMB with the annual report.
- Anticipated or unrelated AEs will be handled in a less urgent manner but will be reported to the DSMB, UMB IRB, and to NCCIH on an annual basis.

Incidents of pregnancy will be reported to all oversight committees along with the annual reports. Participants determined to be pregnant will be withdrawn from the study.

7.5 Follow-up for Adverse Events

At each study visit, the study team will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

The Data and Safety Monitoring Board (DSMB) for this study consists of two research/practicing psychiatrists; one community psychiatrist; one internal and one external biostatistician and one research pharmacist.

The DSMB will 1) review proposed protocols and consent forms prior to the start of enrollment to assess how the PI will report adverse events, early withdrawals and terminations; 2) evaluate recruitment and rate of enrollment in relation to study targets; 3) monitor the occurrence of adverse events, serious adverse events, and early withdrawals or terminations; 4) evaluate study outcomes, when available; 5) monitor study throughout its progress. Any serious adverse event (SAE) that occurs to a subject enrolled in this study will be reported to the DSMB within 5 working days; or within 48 hours if it is directly related to the research intervention. Unexpected adverse events will be reported in accord with NIH and Federal requirements. Non-serious, expected adverse events will be reported annually to the IRB. Once a protocol has been initially reviewed, the DSMB will determine the frequency of review for the study, at minimum yearly.

The DSMB will review with the research team the data management system and study progress. This DSMB has existed for over 10 years and has monitored numerous protocols. The DSMB will receive side effect/adverse event updates whenever this protocol is discussed (although we do not expect any treatment related adverse events since the treatment and the measurements have minimal or no risk). Any serious adverse events (SAEs) will be reported to governing authorities per each agency’s established guidelines.

8. INTERVENTION DISCONTINUATION

The DSMB or IRB will conduct a safety review of AE's and SAE's, which will yield a decision to continue or terminate the study.

Participants may request to be withdrawn from the study at any time, either because of an inability to tolerate the study medication or some other reason. Once a participant is discontinued from the study medication, for whatever reason, we will make every attempt to complete the remainder of the scheduled assessments. This includes laboratory tests and rating scales.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We hypothesize that OEI, compared to placebo, will produce a greater increase in serum butyrate levels secondary to the stimulatory effects of OEI on the activity of known butyrate-producing bacteria.

Our hypothesis will be confirmed if either item 1 or 2 are met:

1. The relative response rate of OEI responders to placebo responders is ≥ 3 for the between group comparison of the end of study post-inulin challenge butyrate level to the baseline post-inulin challenge butyrate level. "Responders" will be defined as those whose change in post-/pre-OEI treatment increases in serum butyrate levels following the inulin challenge is >20%.
2. The effect size of the change in pre-inulin challenge serum butyrate levels between treatment groups is ≥ 0.4 and the relative response rate is ≥ 3, with “responder” defined as a 10% difference in change in serum butyrate levels following the inulin challenge.
    - Note that we will not propose a transition if one of the above biomarker(s) achieves a medium effect size (defined as Cohen’s d ≥ 0.5) in the opposite direction of prediction

If one or the other of the response criterion is met, then we would request a transition to the R33 phase.

9.2 Sample Size and Randomization

Sample Size

The proposed sample size is 20; the participants will be of either sex and any race, and between 18-60 years old. They will meet Diagnostic and Statistical Manual of

Mental Disorders (DSM)-5 criteria for schizophrenia or schizophreniform or schizoaffective disorder.

Treatment Assignment Procedures

The study biostatistician will use a permuted block randomization system (block sizes 2 or 4), in which treatment assignment order is random within each block, with an equal number of participants assigned to each treatment, to generate a list of treatment assignments. Thus, it will be difficult to ascertain the next treatment assignment, even if a participant becomes unblinded, while any imbalance in the number of participants between the treatment groups will be kept within tight limits. All raters, investigators and other staff will be blind to treatment assignment except for the pharmacist. The pharmacist does not participate in the assessment of any of the primary symptom or side effect dependent variables and conveys no information about treatment assignment to participants or staff except in a medical emergency. The non-blind pharmacist will dispense all study medications. The blind will be broken only if a medical emergency requires this information.

9.3 Definition of Populations

All participants who are randomized will be included in the primary outcome efficacy analyses.

All participants who receive at least one dose of the proposed intervention will be included in the safety analyses.

9.4 Interim Analyses and Stopping Rules

We do not plan to conduct interim analyses on any of our primary or secondary outcome measures.

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

9.5 Outcomes

Data collected for this study will be entered into the MPRC research data base using the usual procedures developed for MPRC clinical trials. This study will be reviewed by the UMB IRB and by a Data Safety Monitoring Board (DSMB). The DSMB will evaluate study outcomes when they become available. All members of the committee will be masked to individual participants' treatment assignments.

9.5.1 Primary Outcome

The primary outcome will be the change in serum butyrate levels from baseline to Day 11 (i.e., post 10 days of OEI treatment). We will measure serum butyrate levels on the two inulin challenge test days: a) baseline (Day 0), prior to

randomization to OEI or placebo; and b) Day 11, following the 10-day course of OEI/placebo treatment.

9.5.2 Secondary Outcomes

N/A

9.6 Data Analyses

We will use an intent-to-treat approach to evaluate the change in butyrate production following 10 days of OEI treatment. We will use two approaches to assess the effect of OEI on serum butyrate levels: 1) we will compare end of study to baseline changes in serum butyrate levels following an inulin challenge; and 2) we will compare baseline pre-inulin challenge serum butyrate to end of study pre-inulin challenge serum butyrate levels. A clinically meaningful change in the response to the inulin challenge will be evaluated through the comparison of the relative response rate to treatment; the relative response rate is the ratio of (OEI responders/all OEI participants) to (placebo responders/all placebo participants), and is statistically analogous to calculating the relative risk. We will define "responders" as those whose change in post-/pre-OEI treatment increases in serum butyrate levels following the inulin challenge is >20%. We chose the 20% criterion for responder, because we wanted to minimize the potential for false positives.

We will also evaluate the effect of OEI on serum butyrate levels through the comparison of baseline and end of study pre-inulin challenge serum butyrate levels. We will measure the butyrate levels the morning of the inulin challenge days, prior to the administration of the inulin. All participants will have received the same standardized meal the night before the blood draw.

If the relative response rate of OEI responders to placebo responders is ≥ 3 (e.g. 8 of 10 OEI participants are responders versus 2 of 10 placebo participants are responders), then we would meet our Go/No-go criterion for proceeding to the R33 study. We would have power ≥82% to detect a significant difference in the biological signature between the two groups in the proposed R33 study. If the relative response rate is < 3, then we will examine the change in pre-inulin challenge serum butyrate levels. If the effect size of the change in pre-inulin challenge serum butyrate levels between treatment groups is ≥ 0.4 and the relative response rate is ≥ 3, with “responder” defined as a 10% difference in change in serum butyrate levels following the inulin challenge, then we would consider this adequate evidence for an effect of OEI on our biological signature and would request to proceed to the R33 study.

We will review the extent of missing data for each of the demographic, clinical, and outcome variables. If needed, we will impute missing data by multiple imputation (MI). The assumption of missing at random (MAR) will be used. A sensitivity analysis will be performed to assess the MI.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Blinded research staff, including therapists, a nurse, and a pharmacist, will collect and record information for each participant on the CRF's. Careful procedures will be used to protect the privacy of participants and the confidentiality of the data. Names will only appear on consent forms and on a master list that links them with study ID numbers (different from medical record numbers). This list will be stored in locked files in a separate location from the data. At the conclusion of the project, the list will be destroyed, unless continuation is planned and approved by the Institutional Review Board. All data (whether on forms or electronic data files) will be collected, analyzed, and reported according to the study ID-number and will contain no names or other personal identifiers. Paper-based data will be stored in locked files. Electronic data files reside on desktop computers and are password protected.

10.2 Data Management

Data collected for this study will be recorded on paper Case Report Forms (CRF's), then entered into the MPRC research data base using the usual procedures developed for MPRC clinical trials. This study will be reviewed by the UMB IRB and by a Data Safety Monitoring Board (DSMB). The DSMB will review this study at least annually. If there are any concerns about study safety, then the DSMB may choose to review the study more frequently. Meeting minutes will be reported to the UMB IRB on an annual basis. The DSMB consists of two research/practicing psychiatrists; one community psychiatrist; one internal and one external biostatistician and one research pharmacist.

10.3 Quality Assurance

10.3.1 Training

At the beginning of the protocol, the PI and senior research staff will hold a study Protocol Initiation Meeting (PIM). At this time all study aspects are reviewed and all personnel working on the project attend. This meeting details the procedures of the study. We also develop standard operating procedures for the study and assign a primary research staff member to keep all information up to date. All personnel are told of their role on the study and we hold regular meetings with research personnel to go over study procedures and progress. In addition, all MPRC faculty and staff receive ongoing training on a variety of research issues yearly.

10.3.2 Quality Control Committee

This study will have a Data Safety Monitoring Board. The DSMB will review this study at least annually. DSMB meeting minutes will be sent to the IRB of record and the NCCIH program officer on an annual basis.

Careful procedures will be used to protect the privacy of participants and the confidentiality of the data. Names will only appear on consent forms and on a

master list that links them with study ID numbers (different from medical record numbers). This list will be stored in locked files in a separate location from the data. At the conclusion of the project, the list will be destroyed, unless continuation is planned and approved by the Institutional Review Board. All data (whether on forms or electronic data files) will be collected, analyzed, and reported according to the study ID number and will contain no names or other personal identifiers. Paper-based data will be stored in locked files. Electronic data files reside on desktop computers and are password protected.

10.3.3 Metrics

We will strive to ensure that all participants receive ≥ 90% of their assigned medication. The 90% criterion increases the likelihood that participants will receive adequate treatment to evaluate the effect of OEI on the biological signature. In order to monitor adherence, participants will be observed by research staff while they ingest the study medication. Since all participants will be inpatients, we do not expect problems with adherence, but we will carefully monitor adherence patterns, which will be described within each treatment group as part of any presentation of study results.

10.3.4 Protocol Deviations

Protocol deviations for any reason will be captured on a Study Deviation Log. Failure to follow the protocol due to the action or inaction of the investigator or research staff will be reported to the oversight IRB and the NCCIH program officer within 5 business days.

10.3.5 Monitoring

Designated research staff is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation will be maintained. Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Data entered into the database will be reviewed for completeness and accuracy on a weekly basis. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (Appendix II) will be reviewed and approved by the UMB IRB, who is responsible for oversight of the study. Any subsequent modifications to the protocol will first be reviewed by NCCIH for approval prior to sending them to the UMB IRB for their approval.

11.2 Informed Consent Forms

Research assistants obtaining informed consent will be experienced clinicians. They will receive detailed and standardized training as to how to obtain informed consent from people with serious mental illnesses. They will be observed obtaining informed consent from a study participant by senior staff prior to being allowed to enroll participants on their own.

The consent form will include an explanation of the risks and benefits of participation; assurances of confidentiality; and an explanation that participation is entirely voluntary, the decision to participate will in no way influence or restrict the participants access to clinical services and care at participating sites, and the participant is free to withdraw at any time with no negative consequences. As some potential participants will have poor reading skills, the consent form will be read aloud to all participants in tandem with their own silent reading of the document. The individual securing consent will review any points about which the participant is unclear, and the participant will be invited to ask questions as needed.

11.3 Participant Confidentiality

All research activities will occur in a private room, behind a closed door. Careful procedures will be used to protect the privacy of participants and the confidentiality of the data. Names will only appear on consent forms and on a master list that links them with study ID numbers (different from medical record numbers). This list will be stored in locked files in a separate location from the data. At the conclusion of the project, the list will be destroyed, unless continuation is planned and approved by the Institutional Review Board. All data (whether on forms or electronic data files) will be collected, analyzed, and reported according to the study ID number and will contain no names or other personal identifiers. Paper-based data will be stored in locked files. Electronic data files reside on desktop computers and are password protected.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

N/A

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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15. SUPPLEMENTS/APPENDICES

I. Procedures Schedule

Schedule of Events	2-Week Evaluation Phase	Baseline, Enrollment, Randomization	Double-Blind Treatment Phase		
Encounter # →	P1V1	P2V1	Day1-9	P2V2	P2V3
Day of Study →	Day -14 to -1	Day 0		Day 10	Day 11
Procedure ↓					
Informed consent and ESC	X				
Demographic Forms	X				
Smoking form	X				
SCID-Interview*	X				
Medical History and EKG**	X				
Physical Exam and height**	X				
Dietary Assessment	X				
CMP-14, CBC Lipid Panel	X				X
UA; Urine Pregnancy Test (females)	X				X
BPRS		X			X
HAM-A		X			X
Cytokines, C-reactive protein		X			X
ASCA and AGA IgG		X			X
Tryptophan, Kynurenine, KYNA and 3-HK		X			X
OEI Challenge		X			X
Serum Butyrate: preprandial, 2 hr and 6 hr after OEI challenge		X			X
OEI or Placebo (Day1-10)			X	X	
Vital Signs, including weight, BP and pulse	X	X		X	X
SEC		X			X
Psychotropic and Non-psychotropic Concomitant Medications	X				X

*SCID interview can be re-used if completed within the past 5 years, with the Drug Misuse section re-completed at time of visit.

**Medical history, EKG, physical exam, height and other screening and baseline measures can be collected from the TRP admission assessment if completed within the past 2 months.

II. Informed Consent Form Template

RESEARCH CONSENT FORM

Protocol Title: Prebiotic Treatment in People with Schizophrenia

Study No.: HP-00081820

Principal Investigator: Robert W. Buchanan, M.D.
410-402-7876
Co-Investigator: Deanna L. Kelly, PharmD.
410-402-6861

- Before you agree to participate in this study, it is important that you read and understand the following explanation of the procedures.
- This statement describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study.
- Also described are the other procedures available to you, and your right to withdraw from the study at any time.
- It is important for you to understand that no guarantee or assurance can be made as to the outcome of your participation in this study.
- Please ask as many questions as you like before deciding to participate and during participation in this research study.
- Your participation in this study is voluntary.
- If you are court-ordered for treatment, or a prisoner, your participation in this study will have no effect on your release date, or parole.

PURPOSE OF STUDY

There will be about 30 people enrolled in this study at MPRC/Spring Grove Hospital Center. You are being asked to participate in this study because you have a diagnosis of schizophrenia or schizoaffective disorder.

The purpose this study is to examine if gut bacteria change levels of a fatty acid called butyrate after you receive 10 days of a prebiotic nutritional supplement in a drink or placebo (sugar like powder mixed in a drink); a prebiotic nutritional supplement is a natural plant fiber that beneficially nourishes the good bacteria already in the large bowel or colon.

Thirty patients at Spring Grove Hospital Center (SGHC) will be enrolled in this study; the study is being conducted by researchers from the Maryland Psychiatric Research Center (MPRC). You are being asked to participate in this study because you have a diagnosis of schizophrenia or schizoaffective disorder, and therefore, may have changes in the bacteria that normally live in your intestine. These changes might worsen, or even cause the symptoms of schizophrenia or schizoaffective disorder. The bacteria in your intestines normally produce a small compound called butyrate, which is important for maintaining the healthy functioning of our intestines, and which seems

to positively regulate our immune system, which fights infections and keeps us healthy. People with schizophrenia and schizoaffective disorder have been found to have reduced levels of butyrate, possibly leading to unhealthy intestines, an over-active immune system, and impaired brain functioning. Prebiotin is a natural plant fiber and nutritional supplement that is known to feed the healthy bacteria in our intestines that produce butyrate. By taking prebiotin, we might increase the production of butyrate in our intestines, and thereby improve the health of our intestines, our immune system, and our brain. The purpose of this study is to see if taking prebiotin for 10 days leads to an increase in butyrate in your blood.

PROCEDURES

Overview:

- If you agree to participate you will be enrolled in the study for about 3 and one-half weeks. This will include up to 2 weeks of an evaluation phase, when information is collected to make sure you are eligible to proceed in the study. IF you meet the study requirements, then you will proceed to a 10-day treatment phase.
- You will have your blood work drawn at the beginning and the end of the study. The total amount of blood drawn over the course of the study is approximately 10 tablespoons.
- You will collect stool samples at the beginning and the end of the study
- During the treatment phase, you will take either prebiotin or matching placebo 3 times a day for 10 days AND all participants will receive a prebiotin dose at the beginning and the end of the study.
- Neither you nor your doctor will know whether you are taking prebiotin or placebo for the 10 days in between the two doses.

Description of Evaluation Phase Visit(s): At the first evaluation phase visit, we will perform a standard medical workup including a physical exam, and EKG. We will collect blood for the following laboratory measures: CBC, Chemistry Panel, liver enzymes, and lipid panel. The total blood drawn is about three tablespoons (about 45 ml). A urine sample will be collected for urinalysis and urine pregnancy test (if female). We will ask you questions about your medical, psychiatric, and smoking history. In addition, you will be shown how to collect stool samples. This visit will take about 3 to 4 hours and may be done over two or more days.

Description of the Treatment Phase Visits: If you meet inclusion criteria, you will be randomized to receive either the prebiotic nutritional supplement or placebo. Randomization is like the flip of a coin (a "50-50 chance") to determine whether you will be given the prebiotic or placebo. You will be given the prebiotic nutritional supplement, 3 times a day, with each of your meals, for 10 days. Your weight, height and vital signs (i.e., heart rate, pulse, and blood pressure) will be assessed at the beginning and end of the 10 days. You will also have approximately 2 stool samples collected at the beginning and end of the 10 days.

In order to evaluate the impact of the prebiotic treatment on butyrate levels, we will test the ability of your gut bacteria to produce butyrate before and after treatment. There will be two test days: a) prior to treatment with prebiotic or placebo; and b) following the 10 day course of prebiotic or placebo treatment. On the night prior to the test day, you will receive a completely digestible and low fiber, e.g. lasagna. You will then fast from midnight until the morning, when you will receive your standard breakfast and a 12 gram dose of the prebiotic. Prior to your meal, we will collect blood for the following laboratory assessments: blood markers of inflammation, intestinal lining leakiness, and butyrate. Two and 6 hours after your meal, we will collect blood samples for butyrate. You will

receive a light, low fiber meal 4 hours after you receive the prebiotin. ALL participants will receive the prebiotin dosing at baseline and endpoint.

We will repeat the same procedures after you complete the 10 day course of either the prebiotic or placebo. If any of these measures come back positive, then we will refer you for medical follow-up with the appropriate specialist, even if your participation in the study has ended. Any follow-up treatment with a specialist will not be part of the research study and you or your insurer will be responsible for any costs related to treatment. Please initial yes or no if you agree or do not agree to be contacted about follow-up treatment after your study participation has ended.
Yes_____ No_____

At the beginning of each test day, we will ask you questions about your symptoms. The total blood drawn for each test day is about five tablespoons (about or 75 ml.). At day 11, you will have a urine sample collected for analysis and if you are female, you will also have a urine pregnancy test completed. The total time for each test day visit will be about 7 hours.

WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?

If you take part in this research, you will be expected to: attend study visits as scheduled, consume the prebiotic or placebo as scheduled, follow protocol diet, allow for the drawing of blood samples, cooperate with obtaining stool samples, and take part in the study assessments.

POTENTIAL RISKS/DISCOMFORTS:

The major risks of this study are the risk for embarrassment from the collection of stool samples. You may have discomfort and bruising from the blood draw. You may find the symptom ratings and tests stressful, and possibly frustrating, boring, or upsetting. You may experience some embarrassment discussing personal information during interviews. You may ask to take a break at any time.

We are protecting your personal information but there is still a small risk that your research records would be viewed by someone not authorized to see it. To minimize this risk of someone being able to access your personal information, your research records will be kept in a secure location.
The prebiotic supplement is not absorbed into the body, but may cause gas or stomach discomfort in some people.

POTENTIAL BENEFITS

By providing blood and stool samples as part of the study, you may learn of abnormal results and be referred for treatment for conditions which would have otherwise gone undetected or evaluated. There is also the possibility that there will be no direct benefit from participating in the study, however the following clinical and research-related benefits may occur:

1) Potential clinical benefits for participation in the trial that are not present independent of study participation:
    a) You will have additional meetings with clinical and research staff for psychiatric symptoms and information and evaluation of study participation
    b) You will have access to life skills, illness education group, cognitive behavioral therapy and if a woman, women's trauma group during your stay

c) You have the opportunity to spend Day 0 and Day 11 in the research suite. This provides access to private lounge, videogaming, quiet space and private time
d) You will receive counseling on diet and can participate in healthy cooking groups

2) Potential research-related benefits for participation in the trial that are not present independent of study participation
    a) You will have extra visits for clinical symptom ratings. These include assessment of positive and negative psychiatric symptoms and assessments for anxiety symptoms. These are not routinely completed. The doctors will receive your full results of the symptom ratings and may help your doctor plan better treatment
    b) You will receive standard study assessments that are above and beyond routine care. These include EKG, additional vital signs and bloodwork
    c) You will be monitored daily for diet and food intake and the clinical staff will have access to full accountability of food intake for better and more personalized treatment planning
    d) You will have blood drawn for inflammatory markers (cytokines) and markers for the gut permeability. These are not routine laboratory measures. These results will help clinicians know if inflammation may play a role in your illness and if additional treatment strategies could potentially help their psychiatric symptoms.
    e) You will have a detailed medical history completed and have daily observation. You will receive referrals for advanced care if needed from any clinical or research findings.
    f) You will learn about prebiotin and will receive information about how to get this treatment if they wish to continue outside of the study.
    g) You will have assessments for adverse effects. This will include a private interview and asking of 25 adverse effects. These may or may not be study related but allows for you to discuss all issues you may be having and adverse effects that you are dealing with. This information will help your doctor better address your problems which may not have been addressed previously. This may include constipation, indigestion, enuresis, etc.

Additionally, researchers may increase their understanding of whether, and how the activity of bacteria in the intestines affects the symptoms of schizophrenia. Your bowel movements may be more regular while taking the prebiotic nutritional supplement. This benefit could occur in either group as both will receive prebiotin at some point in the study.

ALTERNATIVES TO PARTICIPATION

You may choose not to participate in this study. If you choose not participate in this study, your treatment at any facility or clinic including MPRC and Spring Grove Hospital will not be affected.

You will be informed in a timely manner of any new findings which may affect your willingness to participate in this study.

COSTS TO PARTICIPANTS

It will not cost you anything to take part in this study.

PAYMENT TO PARTICIPANTS

You will receive $75 for completion of the evaluation phase visits and $50 for completion of the double-blind study visits. The total payment for study completion is $125.

You will be paid by cash or check. If paid by cash, then you will be paid at the end of each visit. If paid by check, then it may take up to 4-6 weeks to receive payment.

CONFIDENTIALITY AND ACCESS TO RECORDS

All forms with information about you will have only a code number and your initials, not your full name. With some exceptions, information that identifies you will not be given to people who are not working on this study, unless you give permission.

When you sign this consent form, you are letting us use your screening data (the information you provided when being screened for this study). Your signature also allows us to use the data that we collect during the study itself. We also ask for approval to contact you again in the future about this study, or other studies you may qualify for. Please initial yes or no if you agree or do not agree to be contacted.
Yes_____ No_____

The data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted auditors may be allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential.

Efforts will be made to reveal your personal information, including research and medical records, only to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization. The monitors, auditors, and the IRB will be granted direct access to your medical records for verification of the research procedures and date. By signing this document, you are authorizing this access.

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.

RIGHT TO WITHDRAW

Your participation in this study is voluntary. You do not have to take part in this research. You are free to withdraw your consent at anytime. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are otherwise entitled and will not adversely affect your treatment at MPRC, University of Maryland or Spring Grove Hospital. If you decide to stop taking part, if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the principal investigator, Robert W. Buchanan at 410-402-7876.

There are no adverse consequences (physical, social, economic, legal, or psychological) of your decision to withdraw from the research. If you wish to no longer participate in the study, please notify a member of the research team. The results from the research will not provide information on your health. You will not receive any individual results.

If you withdraw from this study, already collected data may not be removed from the study database.

CAN I BE REMOVED FROM THE RESEARCH?

The person in charge of the research study, the medically responsible physicians or the agencies that monitor the study can remove you from the research study without your approval. Possible reasons for removal include failure to follow instructions of the research staff, if the person in charge decides that the research study is no longer in your best interest, or you are unwilling or unable to comply with the research schedule. The study doctor will tell you about this and you will have the chance to ask questions if this were to happen.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland, Baltimore (UMB) is committed to providing participants in its research the rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. This research has been reviewed and approved by the Institutional Review Board (IRB). Please call the Institutional Review Board (IRB) if you have questions about your rights as a research subject.

Participating in research may result in an injury, as explained above. If you suffer an injury directly related to your participation in this project, UMB and/or one of its affiliated institutions or health care groups will help you obtain medical treatment for the specific injury and provide referrals to other health care facilities, as appropriate. UMB and/or its affiliated institutions or health care groups will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. The institution or group providing medical treatment will charge your insurance carrier, you, or any other party responsible for your treatment costs. If you incur uninsured medical costs, they are your responsibility. The study staff can give you more information about this if you have a study injury.

By signing this Consent Form, you are not giving up any legal rights. If this research project is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury.

If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland Baltimore
Human Research Protections Office

620 W. Lexington Street, Second Floor
Baltimore, MD 21201
410-706-5037

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

_____	_____
Participant's Signature	Designee Obtaining Consent Signature
Date:_____	Date:_____
_____	_____
Investigator	Witness
Date:_____	Date:_____

III. Data Safety Monitoring Board (DSMB) Roster

MARYLAND PSYCHIATRIC RESEARCH CENTER
DSMB BOARD MEMBERS

Chair:

SAaronson@sheppardpratt.org
Scott Aaronson, M.D. is the Director of Clinical Research Programs at Sheppard and Enoch Pratt Hospital.

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Charles Richardson, M.D. is a Spring Grove Hospital psychiatrist who is in charge of the Inpatient Treatment Program

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Julie Kreyenbuhl, Pharm.D., Ph.D. is a pharmacologist and currently a UMB, IRB Board Member as well. She is the Associate Director, Research Core of the VA VISM 5 MIRECC

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Clayton H. Brown, Ph.D. is an Associate Professor in the Department of Epidemiology, UMB School of Medicine. Dr. Brown is also the Director of the Biostatistics Core for the V.A. Capitol Healthcare Network MIRECC

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