NCT02504151

Cannabidiol Treatment in Patients With Early Psychosis

Study Protocol and Statistical Analysis Plan 5/17/2017

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2013-1)

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Cannabidiol treatment in patients with Early Psychosis			
Principal Investigator: Mohini Ranganathan, MD		**Yale Academic Appointment:** Assistant Professor	
Department: Psychiatry			
Campus Address: Connecticut Mental Health Center, Clinical Neuroscience Research Unit, 34 Park St. New Haven, CT 06519			
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Protocol Correspondent Name & Address (*if different than PI*): Madison Dykins			
Campus Phone: 203-932-5711 x2526	**Fax:** 203-937-4860	**E-mail:** Madison.dykins@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*): N/A			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :** ☒	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) **NA**	**Yale Academic Appointment:**

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Campus Address:

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Campus Phone:	Fax:	Pager:	E-mail:

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

Yes X No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

Yes X No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center ☐ Yale University PET Center

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(MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:

☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:
☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☒ Clinical Neuroscience Research Unit (CNRU)
☒ Other Locations, Specify: Institute of Living, Hartford Hospital
☐ International Research Site

☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☒ Veterans Affairs Hospital, West Haven

(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☒ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 3 years

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☐ Pilot ☐ Phase I ☒ Phase II ☐ Phase III ☐ Phase IV

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☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☒ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)? Yes ☒ No ☐

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☐ No ☒

If you answered "yes", this study will need to be set up in OnCore Support
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

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8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes_No _X_ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

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SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

_____ _____

Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

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SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

This is a four week, randomized, placebo controlled, crossover trial comparing cannabidiol (CBD) to placebo in outpatients with psychotic disorder within their first five years of disease onset. We hypothesize that treatment with CBD will result in:

a. Primary Hypotheses:
   i. Improvement evidenced by a reduction in scores on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS).
   ii. Improvement evidenced by a reduction in the Clinical Global Impression of Severity scale (CGI).
b. Secondary Hypothesis:
   i. Greater improvement in functioning as measured on the "Patient Assessment of Own Functioning Inventory: (PAOFI) and the Quality of Life Scale (QLS)
   ii. No worsening of depressive symptoms or suicidality as measured on the CDSS and CSSRS.
c. Exploratory Hypotheses:
   i. Exploration of the effect of CBD on EEG recordings of MMN and P300 amplitude and latency, known endophenotypes/biomarkers of Schizophrenia

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

There is a need to develop anti-psychotic therapeutics with novel mechanisms of action and fewer side effects:

Current first and second generation anti-psychotics employ a common mechanism of dopamine receptor antagonism leading to varying degrees of motor side effects and QTc prolongation for the class as a whole. Second generation anti-psychotics have also been demonstrated to cause significant metabolic side effects including weight gain, dyslipidemia, and diabetes mellitus [1-3]. Specifically, the CATIE study found the prevalence of metabolic syndrome in schizophrenia to be 42% compared to 23% in the general population [4]. Given the significant morbidity and mortality associated with schizophrenia, even appropriate treatment with the currently available medications has the potential to add serious medical illness to an already poor prognosis [4, 5]. *Thus, it is imperative that new antipsychotics with novel mechanisms of action be developed not only to find more tolerable therapies for this high risk group but also to address the significant portion of patients with incomplete response and potentially those with psychotic symptoms derived from neurodegenerative disease [6].*

Cannabidiol, a component of herbal cannabis, may have antipsychotic effects via a novel mechanism of action:

Cannabidiol is a component of herbal cannabis, studied for a number of potential pharmaceutical indications since the 1970s given its purported hypnotic, anticonvulsant, neuroprotective and hormonal effects [7-10]. More recently, enthusiasm has mounted surrounding its potential as an anti-psychotic and anxiolytic. Initially thought to be a CB-1 antagonist, the mechanism of action

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of cannabidiol has more recently been thrown into question. Various alternative mechanisms have been suggested including modulation of the endocannabinoid system via FAAH inhibition leading to increased levels of the endogenous cannabinoid, anandamide, TRPV1 activation, 5-HT1A agonism, and NMDA receptor modulation [11-13]. Overall, the true mechanism of action remains unknown. Studies have proposed that alterations in the endocannabinoid system, manifesting as significantly elevated levels of anandamide in the cerebrospinal fluid of schizophrenic patients, may suggest a protective role of this compound against psychosis, one that cannabidiol may modulate in therapeutically significant ways not yet fully understood. Brain imaging studies also demonstrate opposite effects of CBD and THC in particular brain regions thought to be associated with the development of psychosis. Specifically, fMRI studies have demonstrated CBD's augmentation of activity in the right posterior temporal gyrus, the left caudate and the hippocampus as well as attenuated activity in the right prefrontal area, all of which are the opposite of THC effects [14]. Despite the lack of clarity regarding its exact mechanism of action, clinical studies in both human and animal models have suggested antipsychotic effects as discussed below, with an extremely favorable side effect profile.

Cannabidiol has been shown to exhibit antipsychotic effects:
Within the last decade, animal models have demonstrated CBD's ability to decrease hyperlocomotion induced by amphetamine and ketamine and to extinguish stereotyped behavior induced by apomorphine in rats [10, 15]. Human case studies also suggested antipsychotic effects of CBD in patients unable to tolerate or unresponsive to usual therapies. While the exact mechanism of action remains unknown, more recent clinical studies have demonstrated that pre-treatment with CBD inhibits the psychotomimetic effects of THC resulting in a significant decrease in self-reported paranoia and a non-statistically significant trend toward decreased PANSS scores [16]. Indeed, a high ratio of THC to CBD has been correlated with increased risk of psychotic symptoms further suggesting a protective role of CBD, at least among cannabis users [17, 18].

Perhaps most encouraging was a recent clinical trial by Leweke, et al. which showed similar reduction in PANSS scores in patients treated with CBD versus the D2/D3 antagonist amisulpride [11]. In this double blind parallel group randomized active controlled clinical trial, men and women aged 18-50 with acute exacerbation of schizophrenia or schizophreniform psychosis received four week courses of either cannabidiol or amisulpride with recording of baseline, day 14 and day 28 PANSS scores. Side effects were also measured using the Extrapyramidal Symptom Scale. Results revealed a similar reduction in PANSS scores in both groups, no difference in the percentage of responders and significantly fewer extrapyramidal side effects in the CBD group. This promising evidence for likely non-inferiority of CBD warrants replication as well as investigation of its use outside the acute stage and in the outpatient setting, which the proposed study intends to investigate. Furthermore, the addition of objective outcome measurements including psychosocial, cognitive, mood, and biomarker data as well as the use of a wider range of cannabidiol dosages would contribute to the overall picture of CBD's use as a novel anti-psychotic.

Cannabidiol has few side effects and is generally well tolerated:
Based on earlier studies of the 1970s, Cunha et al. demonstrated that 300-400mg daily doses of cannabidiol for 30 days in healthy subjects as well as 100-200mg daily for 4.5 months in subjects with epilepsy revealed no adverse effects beyond mild somnolence [19, 20]. High doses of the

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medication were also well tolerated in case studies of use in patients unable to tolerate or resistant to dopamine antagonists and in doses up to 10mg/kg (average of 700mg) daily for 6 weeks in patients with Huntington's Disease and in combination with alcohol [21-23]. Specifically, analysis of reported side effects in the latter study showed no significant difference between placebo and CBD [22]. Also, in the aforementioned trial comparing anti-psychotic effects of CBD and amisulpride, patients treated with cannabidiol had a significantly fewer extrapyramidal symptoms, less weight gain, and lower prolactin levels [11].

Individuals early in their course of illness may particularly benefit from treatment with a medication such as cannabidiol:
In treatment settings caring for patients with early psychosis, ~30% drop out of care within the first year which may be related to unwillingness to tolerate medication side effects associated with dopaminergic antipsychotic medications. As discussed above, CBD is very well tolerated and may thus be a suitable choice especially in early psychosis when patients are medication naïve and more sensitive to the side effects. Furthermore, these individuals typically have high rates of cannabis use (~30%) in this cohort, which is associated with worsening of symptoms, course and engagement with treatment. CBD, in laboratory studies has been shown to attenuate the effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis and may potentially have benefits in this population. Furthermore, since CBD is known to be a component of cannabis, patients may have fewer reservations about accepting this as a treatment.

Thus, given some evidence supporting the antipsychotic potential of CBD, its effects on non-specific symptoms such as anxiety and insomnia and its favorable side effect profile, further study of CBD's anti-psychotic effects may benefit from inclusion of more objective measures such as Event Related Potentials (ERPs).

ERPs are oscillatory brain responses seen on EEG triggered by particular stimuli. Numerous studies have demonstrated aberrations in event-related potentials in schizophrenia, specifically deficient mismatch negativity (MMN) and significantly decreased P300 amplitude and latency which are hypothesized to serve as indices of abnormal auditory sensory memory, information processing speed and allocation of attention ([24-26]. A recent study by Fisher, et al. demonstrated both a correlation between decreased MMN and increased PANSS scores as well as a correlation between decreased P300 amplitude and increased auditory hallucinations [25]. Attenuation of the MMN and decreased P300 measures have thus been suggested as endophenotypes of schizophrenia and potential biomarkers of disease [24, 27]. Studies assessing the effects of medications on the MMN and P300 are limited. While clozapine use has been associated with increases in P300 amplitude, first generation anti-psychotics and olanzapine have not [28, 29]. However, further research on the use of biomarkers to assess medication effect is needed and collection of this data will shed light on the potential role of antipsychotics and CBD in particular on normalizing these processes.

Significance:
As outlined above, CBD has shown potential anti-psychotic effect via novel mechanisms of action as compared to the currently available drugs. CBD is likely to have an extremely favorable side effect profile. There is a need for novel anti-psychotics both to expand upon the currently available, effective battery of therapeutics and to limit the medical comorbidity associated with current therapies.

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Consent Procedures: Subjects who meet entry criteria will be invited to meet with the research staff, who will fully explain risks and procedures as outlined in the consent form. After reviewing this information and answering questions, informed consent will be obtained from all subjects. A copy of the consent form will be provided to all subjects.

Medical and Psychiatric Evaluation: Once written informed consent has been obtained, the diagnosis will be confirmed by a Structured Clinical Interview for DSM IV (SCID). A detailed medical and psychiatric history, physical examination (including vital signs, height, and weight), an electrocardiogram, and laboratory assessments (standard screening blood tests: CBC with differential and platelet count, electrolytes, creatinine, BUN, liver enzymes, T4, calcium, phosphate, TSH, and magnesium levels) will be performed. In addition, a full lipid profile, fasting glucose and insulin levels will be obtained. A pregnancy test will be done in all premenopausal women. A routine urinalysis and drug screen will be done as part of the screening process.
Subjects will be administered the PANSS and motor side effects scales (AIMS, Barnes akathisia scale, Simpson Angus scale). IQ will be measured at screening using the Wechsler Test of Adult Reading (WTAR). Subjects will also be asked to provide an informant who can be contacted to collect clinical and safety information relevant to the outcome measures on each visit. This could be a clinician or a family member/friend who sees the patient at least on a weekly basis.

Study Design: In this 2 period cross over design, subjects will be randomized in a 1:1 ratio to receive either: **Order 1**: CBD (Period 1) followed by placebo (Period 2) or **Order 2**: Placebo (Period 1) followed by CBD (Period 2) under double-blind conditions. The 2 study periods will be separated by a washout of at least 2 weeks. During each period subjects will receive study medications (CBD [total 800mg/day] or placebo) for a period of 4 weeks. This dose is within the dose range of doses that have been shown to be effective and safe. Randomization to the order of medication assignment will be stratified by baseline PANSS scores.

Study Visits:
Subjects will have the following visits during each period except for Visit I (screening), which will occur only at the beginning of their participation in the study:
Visit I: Screening (At least two visits: Visit Ia and Visit Ib.)
Visit II: Baseline: Will initiate treatment with study drug following baseline assessments.
(Visits III, IV, V: Weekly clinical evaluation and study medication refill)
Visit III: (Week 1)
Visit IV: (Week 2)
Visit V: (Week 3)
Visit VI: (Week 4): End of treatment period visit
Visit VII: Safety Follow up at week 5.
Visit VIII: One close-out visit will be conducted after Visit VII in Period 2 for lab review and safety follow up.
Note: Visits II-VI can be split into two visits, which must be completed within +/- 3 days of each other based on the subject's availability.

Outpatient Medication Compliance: Medication compliance will be monitored throughout each study period by self-report and vial counts at study visits and using the *Cellphone Assisted*

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Remote Observation of Medication Adherence (CAROMA). CAROMA may be used 1-2 times per day during the treatment period to confirm compliance. Flexible scheduling will be maintained regarding time and days of CAROMA depending on subject reliability, availability and frequency of in person visits. Subjects will be provided with a cellphone with the hardware, software and service necessary to transmit high quality video. Prior to randomization, the subject will be trained how to use the phone and also trained on the compliance protocol. For this, the subject will be placed in one clinic office with the phone. A research staff member will video call the subject from another location in the clinic and observe the subject consuming a syringe of water. Once successfully trained in the clinic, the subjects will be loaned the phone to take home for one trial CAROMA visit. This is to ensure that 1) the in-clinic training extends to the home, and 2) that the subject has adequate cellular service at home. Within a time period predetermined by agreement, subjects will be called on the cell phone and will be observed removing study medication from the packaging and swallowing the medication. The research assistant will log visual confirmation of compliance. Subjects will receive additional compensation for CAROMA visits as outlined in the "Economic Considerations" section below. Subjects who are not contactable will be assumed to be noncompliant for that visit and will not receive payment for the missed CAROMA visits.

Finally, compliance will also be confirmed by measuring CBD levels in plasma from blood sampled at regular intervals throughout the study.

Study Procedures:

Safety Assessment: during each visit. This will include assessment of psychiatric status, assessment of adverse events, vital signs, and safety labs (CBC, Chem 19, urinalysis, and urine toxicology).

Outcome measures:

1. **Positive and Negative Syndrome Scale** (PANSS) (Visits I-VI): The PANSS includes 3 scales and 30 items: 7 items that make up the Positive Scale (eg, delusions, conceptual disorganization, hallucinatory behavior); 7 items that make up the Negative Scale (eg, blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal); and 16 items that make up the General Psychopathology Scale (eg, somatic concern, anxiety, guilt feelings, mannerisms and posturing, motor retardation, uncooperativeness, disorientation, poor impulse control, preoccupation). Individual items are scored with values ranging from 1 to 7.

2. **Personal and Social Performance Scale (PSP)** (Visits I-VI): The PSP scale is a validated clinician-related scale that measures personal and social functioning in the domains of: socially useful activities (eg, work and study), personal and social relationships, self-care, disturbing and aggressive behaviors. Information from the subject and the informant will be utilized in determining the rating. The interview with the informant may be conducted by phone once the initial in-person interview has occurred and informed consent has been obtained.

3. **Clinical Global Impression (CGI) (Visits I-VI):**
    a. **Clinical Global Impression of Severity (CGI-S):** The CGI-S consists of a single 7-point rating score of illness severity. Raters select one response based on the following question, "Considering your total clinical experience with this particular population, how mentally ill is your patient at this time?" Scores are: 1, Normal, not

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ill at all; 2, Borderline mentally ill; 3, Mildly ill; 4, Moderately ill; 5, Markedly ill; 6, Severely ill; or 7, Among the most severely ill subjects.

b. Clinical Global Impression of Improvement (CGI-I): The CGI-I consists of a single 7-point rating score total improvement, regardless of whether or not the change it is due entirely to drug treatment. Raters select one response based on the following question, "Compared to your patient's condition at the beginning of treatment, how much has your patient changed?" Scores are: 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse. **For the CGI-I Scale, the subject's condition at the Day 1 (Baseline) visit will be the criterion for judging improvement at subsequent visits.**

4. **Columbia Suicide Severity Rating Scale (CSSRS) (Visits I-VI):** The CSSRS is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior. Versions are available for Screening/Baseline and follow-up visits.

5. **Quality of Life Scale (QLS) (Visits II-VI):** The QLS is a structured interview providing clinician ratings of function in key areas of everyday living.

6. **The Patient Assessment of Own Functioning Inventory: (PAOFI) (Visits II-VI):** will be included as a subjective assessment of cognitive functioning. The PAOFI is a widely used self-report instrument that taps into the respondent's own views and experiences regarding difficulty in everyday functioning.

7. **Motor side effect scales (Visits I-VI):** Barnes Akathisia Scale, Simpson Angus Scale, and the AIMS; Further, the UKU side effects scale will be administered at weekly visits to assess for antipsychotic induced side effects.

8. **Metabolic parameters (Visits I, II, IV, VI):** Appetite and food intake ratings (VAS) and three day dietary record (which have been shown to be predictors of energy intake and weight loss [30]), weight, fasting glucose and lipid profile.

9. **Smoking and Cannabis use (Visits I-VI):** Past week Time Line Follow Back approach.

10. **EEG testing:** The main EEG outcome measures will be P50, P300 and ASSR as discussed above. Brain wave activity during tasks involved in the processing auditory and visual stimuli with different degrees of attentional and memory demands will be recorded. Auditory stimuli will include tones, white noise bursts, other digitized sounds (such as dog barks, rooster crows), or spoken words. Visual stimuli will include letters, numbers, words, geometric shapes, colored patterns, or photographic images. Some audiovisual stimuli may have emotive/emotionally salient or neutral content. Stimuli will be separated by intervals of .5 to 30 seconds. Some stimuli will require a button-press response using a response pad. These may be target stimuli in target detection tasks, or recalled stimuli in memory tasks. The EEG session will last approximately 2 hours.

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On the testing days (Visit II and Visit VI), participants will be brought to the EEG testing booth. In the EEG recording, an elastic cloth cap with Ag/AgCl electrodes is worn by the subject. A conductive gel is then placed between the skin and the electrode prior to recording. The subject will then listen to sounds or view visual images produced by a computer. By varying the characteristics of the auditory and visual stimulation, different brain systems are activated. In some recordings, the subject will be asked to press a button to indicate what sort of stimulation he or she experienced. The EEG recordings will be obtained using a commercial psychophysiological system. The entire EEG procedure will take approximately 1.5 hours.

EEGs will be recorded at a sampling rate of 1024 Hz with on-line low-pass filter of 256Hz to prevent aliasing of high frequencies. A 64-channel electrode cap according to the extended 10-20 system will be utilized. Seven additional electrodes will be placed: two on the mastoid processes, two horizontal EOG channels lateral to the left and right eyes' lateral canthi, two vertical EOG channels, one below (infraorbital) and one above (supraorbital) the right eye, and a channel on the tip of the nose. All electrodes will be referenced during recording to a common-mode signal (CMS) electrode between POz and PO3 and will be subsequently re-referenced digitally. A conductive gel will be placed between the skin and the electrodes prior to recording. The cap and all electrodes that come into contact with the skin will be cleaned and disinfected after each use in an antibacterial soap, which kills almost all vegetative microbial and viral life forms.

The main dependent measures of the EEG portion of the study will be traditional EEG waveform amplitude and latency. Secondary measures will be EEG spectral power, inter-electrode coherence, and inter-trial coherence.

11. **CBD and Endocannabinoid Levels:** Blood will be drawn at visit II-VI for plasma CBD and Anandamide levels. CBD levels will be assayed by our collaborator, Thomas Cooper, at Nathan Kline Institute. Serum Anandamide levels will be assayed by our collaborator, Alex Makriyannis, Director, Center for Drug discovery at Northeastern University.

12. **Neuropsychological Testing (Visits I, II, and VI):** A cognitive battery will be utilized to assess working memory, spatial working memory, episodic memory, and learning.

Drug Dose and Administration: CBD will be used under IND# 126731 and supplied by Insys Pharmaceuticals Ltd. with a shelf life of 1 year. The product will be stored in the Veterans Affairs Connecticut Healthcare System pharmacy in West Haven, CT as per package instructions. The investigators brochure from Insys Pharmaceuticals is submitted along with this application. Pharmacists will deliver medication vials to study staff for dispensing by study psychiatrists. The daily dose for this study is CBD 800mg in an oral solution. This dose has been previously shown to be well tolerated in healthy subjects as well as schizophrenia patients in a recent clinical trial of 42 patients who were treated with CBD 800 mg vs. Amisulpiride for 4 weeks [11].

3. Genetic Testing N/A ☐

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A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned

Depending on the future course of the project and the results of the work, genome wide (GWAS) genotyping, full exome sequencing, or full genome sequencing – or some intermediate stage between these – may be employed. Results from these subjects may be compared to other subjects that we or our collaborators have recruited or may recruit in the future in the course of this project or other projects; or other publicly-available data. We will consider any phenotypes about which information can be collected, concentrating, however, on psychiatric diagnoses, imaging measures, and response to treatment.

ii. the plan for the collection of material or the conditions under which material will be received

Samples will be drawn at the Connecticut Mental Health Center, the West Haven Va and the Institute of Living and transported to the West Haven VA for storage via Yale's Intracampus Transport system.

iii. the types of information about the donor/individual contributors that will be entered into a database

No identifiers will be entered in the database.

iv. the methods to uphold confidentiality

Discussed on pages 20 and 32-33.

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?

N/A, as below.

C. Is widespread sharing of materials planned?

No, there is not.

D. When and under what conditions will materials be stripped of all identifiers?

All biological materials studied in the DNA lab will have been stripped of any personal identifiers. Keys that can be used to match subject with genotype (and personal ID) will be retained indefinitely.

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E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?

Yes, subjects are free to withdraw their identifiers at any time.

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

At subjects' request, samples will be de-identified, however, we will continue to study genotype and phenotype data together.

F. Describe the provisions for protection of participant privacy

Bloods for genetic analysis will be collected at the screening visit and stored until analyzed. The laboratory will receive no identifying information about the samples. A key linking the samples with identifying information will be stored in Dr. Ranganathan's laboratory.

G. Describe the methods for the security of storage and sharing of materials

The genetic materials will be stored indefinitely for future study including genome-wide association studies. There are no plans for sharing the samples. Participants can withdraw their identifiers at any time.

4. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Subjects with a diagnosis of Schizophrenia Spectrum Disorder will be recruited. The study aims to enroll patients with psychosis who do not currently require an inpatient hospitalization. We will attempt to enroll a significant portion of patients whose current treatment does not include anti-psychotic medication. Target sample size is 36. Expecting a screen failure rate of 50%, we will enroll up to 72 subjects to achieve the target sample.

5. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☒ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

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6. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

1. Primary psychotic disorder (Schizophrenia, Schizoaffective disorder, etc.)
2. Age 18-65
3. Capable of providing informed consent
4. Within approximately five years of onset of psychosis/ presentation to treatment for psychosis

Exclusion Criteria:

1. Other current major psychiatric diagnoses that require pharmacological treatment (example: PTSD). Some diagnoses will be allowed at the PI discretion (example: Adjustment disorder)
2. Current substance dependence (other than nicotine or cannabis)
3. Serious medical or neurological illness or treatment for a medical disorder that could interfere with study participation as determined by principal investigator
4. History of significant head injury/trauma as determined by principal investigator
5. Women who are pregnant, nursing or unwilling to use appropriate birth control measures during study participation
6. Inability to complete neuropsychological tests
7. History of treatment resistance or current treatment with clozapine
8. Current treatment with investigational agents or participation in another clinical trial that may affect outcome measures

7. How will **eligibility** be determined, and by whom?

Subjects may first undergo a phone screen to initially determine eligibility. Information collected during the phone screen will only be used in the event that the subject continues to participate in the study.

After determining initial eligibility, research staff will provide a brief description of the research and the subject will present to the clinic for the screening procedures described above. Once all screening procedures have been collected, research staff as well as the principal investigator will review all relevant information and determine, based on the inclusion and exclusion criteria, if the subject will continue with the remaining study procedures. Subjects already on antipsychotics or other medications will continue use of the medications while participating in the current study. Subjects will not be taken off their antipsychotic medications for participation in this study.

8. **Risks:** Participation in this study may be associated with risks related to:

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a. **Psychiatric evaluation:** Subjects will undergo a Structured Clinical Interview for DSM-IV conducted by a research assistant and a psychiatric and medical evaluation during screening. The diagnostic interviews may cover issues, which are stressful to a person, for example, questions regarding the experience of paranoid thoughts or social isolation. Thus, they may experience some distress during these interviews.

b. **Loss of confidentiality:** Participation in research may involve a loss of privacy and confidentiality. Therefore, extensive measures are in place to protect the confidentiality of subjects. (See below.)

c. **Study assessments:** During the baseline and follow-up assessments, study participants may become tired or frustrated. If this occurs, they will be encouraged to take breaks. It is also possible that some individuals may experience discomfort during the interviews, when they are asked to talk about their psychiatric symptoms. Subjects may feel bored, tired, exhausted, discouraged or distressed by the questionnaires or EEG testing.

d. **CBD administration:** CBD is a naturally occurring component of cannabis that has been used recreationally and for medicinal purposes by large populations. As mentioned above, studies have shown good tolerance of cannabidiol even in high doses with relatively few side effects and no known severe events. Sedation and/or lightheadedness are likely to be the most common reported adverse reaction. Patient will be assessed weekly for the development of side effects.

e. **Worsening of psychosis:** Participation in this study may be associated with worsening of psychosis especially in those individuals who are not on any other antipsychotics. Subjects will be evaluated on a weekly basis in face-to-face meeting with study staff. Psychotic symptoms, mood symptoms and suicidality will be assessed at each of these meetings. Further, subjects will be contacted approximately 5 times per week using CAROMA for the confirmation of compliance. During each of these visits, subjects will be asked if they have noticed any worsening of symptoms or any new side effects. If subjects report that they do notice a worsening of symptoms or side effects, this will be evaluated by an investigator on the team and subject will be asked to come into the clinic to be evaluated if clinically indicated. Subjects are well aware that in case of significant worsening of symptoms/ emergence of SI/HI, they may be escorted to the ER or admitted to an inpatient unit.

f. **Risk of blood draws: B**lood will be drawn weekly during the study to monitor medication levels as well as safety labs. There are usually no serious medical problems with blood drawing, but there may be pain at the venipuncture site or bruising or infection may occur.

g. **Risks of EEG:** EEG is a non-invasive assessment. There are minimal risks associated with EEG/ERP recording. Traditionally, scalp abrasion has been used to improve

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signal impedance at the electrode site. The EEG/ERP system used in this laboratory is a high-impedance system and does not require scalp abrasion to obtain clean recording. A conductive gel is applied, which can be easily washed out of the subject's hair with warm water. A shower facility for hair washing and sterile linens are available in the laboratory. Electrode caps and sensors will be washed and sterilized between subjects to minimize the risk of transmitting infection.

Potential benefits: Subjects will receive no direct benefit from this study. Potential benefits may include improvement in psychotic and cognitive symptoms, decreased negative symptoms, avoidance of potential side effects from usual anti-psychotic medications themselves or from dose increases of such medications. Overall, the development of novel anti-psychotics will provide benefit to the schizophrenia population as a whole.

Risk/Benefit ratio: As described above, the primary risks of this study are related to CBD administration and are low. Extensive safety measures are in place to ensure that participants with worsening psychosis or mood symptoms are identified expeditiously. The overall risk-benefit ratio is therefore favorable.

9. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Loss of Confidentiality: There is a risk of loss of confidentiality in this study. All subject information will be kept confidential and only members of the investigative team with appropriate IRB/HIC and HIPAA training will have access to the study data. Data will be maintained and secured in locked file cabinets or password protected electronic media. A numbering code will be used to assign a unique identifier to each subject. The researchers will be applying for a certificate of confidentiality (COC).
For the Cellphone Assisted Remote Observation of Medication Adherence (CAROMA) procedures, subjects will be called and observed while taking study medications. The CAROMA procedure is not recorded, broadcast, nor will the likeness of the subjects be used for anything other than what has been specified. The potential for loss of confidentiality is if someone taps the phone while a call is being made, but this risk is no different from someone tapping into a phone (audio) conversation between the subject and the research team. The phones used for this practice will be encrypted by Yale University Information Technology Services (ITS) so that loss of confidentiality is minimized. CAROMA was set up with input from Yale ITS in order to conform to Yale's policies.

Psychiatric Evaluation and Study Assessments: If subjects become tired, frustrated, or distressed during assessments or evaluations, they will be encouraged to take breaks.

CBD Administration: Patients will be assessed weekly for the development of side effects. Worsening of psychosis: Subjects will be evaluated on a weekly basis in face-to-face meeting with study staff. Psychotic symptoms, mood symptoms, and suicidality will be assessed at each of these meetings. Further, subjects will be contacted approximately 5 times per week using CAROMA for the confirmation of compliance. During each of these visits, subjects will be asked if they have noticed any worsening of symptoms or any new side effects. If subjects report

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that they do notice a worsening of symptoms or side effects, this will be evaluated by an investigator on the team and subjects will be asked to come into the clinic to be evaluated if clinically indicated. Subjects are well aware that in case of significant worsening of symptoms/ emergence of SI/HI, they may be escorted to the ER or admitted to an inpatient unit.

Risks of Blood Draws: Due to the risks associated with phlebotomy procedures, subjects who have donated blood within eight weeks to the present study will be excluded. Subjects will be told that they should not give blood for at least eight weeks.

Risks of EEG: The risk of irritation during EEG set up will be minimized through careful application of electrodes and appropriate cleansing of the skin by trained technicians.

10. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    - **a.** What is the investigator's assessment of the overall risk level for subjects participating in this study? Moderate risk
    - **b.** If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? No children will be enrolled.
    - **c.** Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal/moderate risk
        iii. High risk

SAFETY: Subjects will be closely monitored for worsening of symptoms or side effects. They will be provided with a 24 hour access to study personnel to discuss any concerns. Subjects will be given a wallet card indicating they are taking experimental medication and directions for how to determine what they are taking in case of an emergency.

Adverse events will be reported to the HIC and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and key study personnel of all serious and unanticipated adverse events that occur during the conduct of this research project. Adverse events will be graded as per HIC policy.

Data safety and monitoring plan: This is a moderate risk study, and no serious adverse events are expected. If any should occur, however, the following grading system will be used to assess the seriousness of the adverse events:

0 No adverse event or within normal limits
1 Mild adverse event
2 Moderate adverse event
3 Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

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4 Life-threatening or disabling adverse event
5 Fatal adverse event

Serious unanticipated adverse events will be reported immediately to the VA Connecticut Healthcare System, Yale University School of Medicine, California Pacific Medical Center institutional review boards and any appropriate funding and regulatory agencies. Serious anticipated adverse events will be reported immediately to the institutional review boards and others whenever their magnitude or frequency exceeds expectations.

The principal investigator will evaluate all adverse events and determine whether the adverse event affects the risk/benefit ratio of the study and whether modifications to the protocol or consent form are required. A summary of the adverse events will be reported to the institutional review boards periodically or, at minimum, when reapproval of the protocol is sought. The summary will include number of subjects enrolled and a summary of graded adverse events to date. All adverse events will be graded using the following grading system:

Attribution	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	UNATP	ATP	UN ATP	ATP	UN ATP	ATP	UN ATP	ATP	UN ATP	ATP
Unrelated										
Unlikely										
Possible										
Probable										
Definite										
Totals										
Total Subjects Enrolled to Date										

The principal investigator will be responsible for monitoring the data and conducting performance of safety reviews at regular intervals, as indicated above. The principal investigator will conduct a data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification, continue or close to enrollment.

DSMB: A Data Safety Monitoring Board is being assembled for this study. Unblinded safety data will be provided to the committee for monitoring purposes, in a meeting that will be held approximately every 6 months. DSMB reports will be provided to the HIC.

11. **Statistical Considerations:**

General Strategy:

All outcomes will be summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses will be performed as necessary. All tests will be two-sided and considered statistically significant at alpha=.05. Post-hoc comparisons will be performed as appropriate and significance levels for secondary analyses will be adjusted for multiple tests using the Bonferroni correction. All analyses will be performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC).

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Linear mixed models will be used assess symptom improvement as measured by the PANSS (primary hypothesis) and CGI. In these models group (CBD vs. placebo) and time (see study time points) will be modeled as within-subjects factor. Oder effects will also be tested. Least squares means and standard errors will be calculated in the mixed model and plotted to interpret significant effect. A significant group by time interaction explained by reduced symptoms over time due to CBD treatment will be supportive of our hypothesis. In the above models, the best fitting variance-covariance structure will be selected based on information criteria. The mixed effects approach is advantageous in that it is unaffected by randomly missing data and allows greater flexibility in modeling the correlation structure of repeated measures data [31]. Similar mixed models as described above will be employed to evaluate secondary outcomes (e.g., PAOFI, EEG parameters).

Power Analysis:
We will recruit 36 subjects and randomly assign 18 to receive either CBD followed by placebo (order 1) or placebo followed by CBD (order 2). Based on a within-subjects design and a two-tailed alpha=0.05, 36 subjects will provide 80% power to detect moderate treatment effects as small as d'=0.49. This compares favorably with the effects (d=0.7) observed by Leweke in their study comparing CBD to amisulpiride in schizophrenia patients.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** The investigational drug to be used in this study is Cannabidiol provided by Insys Pharmaceuticals. This study will be conducted under an IND# 126731.

2. **Background Information:**

Cannabidiol (CBD) is a component of herbal cannabis that is present in varying concentrations in cannabis extracts. CBD has been shown to produce central effects including hypnotic, anticonvulsive, anxiolytic and neuroprotective effects [10]. Until recently, the mechanism of action of CBD was unclear. However, recently, CBD has been found to be a potent non-competitive inhibitor at CB-1 and CB-2 receptors [32] in addition to having effects at a third as of yet unidentified central cannabinoid G-protein coupled receptor.

CBD has also been used to treat patients with schizophrenia. Early case series suggested mixed results but good tolerability even at high doses [9]. Preliminary results from an SMRI funded 4-week, double-blind comparison of CBD vs. amisulpride in acute schizophrenic and schizophreniform psychosis have been promising. CBD significantly reduced acute psychotic symptoms after 2 and 4 weeks of treatment. CBD was equivalent to the amisulpride in efficacy and was also associated with fewer side effects [33].

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3. **Source:** a) Identify the source of the drug or biologic to be used.

   b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
   If yes, by whom? Insys

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

   Check applicable Investigational Drug Service utilized:

   ☐ **YNHH IDS**
   ☐ **CMHC Pharmacy**
   ☐ **PET Center**
   ☐ **Other:**
   ☐ **Yale Cancer Center**
   ☒ **West Haven VA**
   ☐ **None**

   Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

   The material will be stored in the West Haven VA pharmacy as per package insert. Pharmacists will deliver medication vials to study staff for dispensing by study psychiatrists.

5. **Use of Placebo:** ☐ **Not applicable to this research project**

   If use of a placebo is planned, provide a justification which addresses the following:

   a. The study intervention include CBD or placebo. The inclusion of placebo is to permit comparison with CBD. However, we recognize that for an individual with a psychotic disorder the standard of care is treatment with first or second-generation antipsychotic medication. A large proportion of individuals with early psychosis discontinue or never initiate antipsychotic treatment due to a number of factors including fear of side effects, stigma etc. This study CBD versus Placebo will recruit all individuals. This study will not interfere with standard of care and will be in addition to treatment as usual. Due to the prevalent refusal of traditional antipsychotic treatment among individuals with early psychosis we anticipate that some subjects who will receive CBD/Placebo will be on no other medication. However, requiring treatment with traditional antipsychotics or proposing an active control instead of placebo will exclude this proportion of individuals and in fact result in data that is not generalizable to this, most vulnerable population. Safety assessments will be done in person weekly, and multiple times during the week over the phone. Furthermore, subjects will be encouraged to remain compliant with their regular treatment sessions and medications.

      There is no alternative to CBD since its efficacy is unknown. The alternative is not to participate in this trial.

   b. State the maximum total length of time a participant may receive placebo while on the study.

      Four weeks

   c. Address the greatest potential harm that may come to a participant as a result of receiving

placebo.

No improvement in psychotic symptoms or course of illness. Placebo by itself is not anticipated to worsen psychotic symptoms. However, if psychotic symptoms are worsening placebo will not prevent the decompensation.

d. Describe the procedures that are in place to safeguard participants receiving placebo.

Weekly follow up visits and safety assessments including PANSS assessments will be conducted to detect worsening of symptoms.

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ No ☒ Yes *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☒ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☒ No
The use of CBD is experimental. At this point there are no data supporting its use in the treatment of any illness.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒
If Yes, please be aware of the following requirements:

a. A YNHH New Product/Trial Request Form must be completed;

b. Your request must be reviewed and approved by a Hospital Committee before patients may be scheduled; and

c. The notice of approval from YNHH must be submitted to the HIC for the protocol file.

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Please contact Gina D'Agostino, gina.d'agostino@ynhh.org or 203-688-5052, to initiate the process.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**

a) Identify the source of the device to be used.

b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

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6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:
   b. Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol
   Approximately 70 to have 36 completers
   b. If this is a multi-site study, give the total number of subjects targeted across all sites_N/A__

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers
☐ Posters
☐ Letter
☐ Medical Record Review
☐ Departmental/Center Newsletters
☐ YCCI Recruitment database
☐ Other (describe):

☒ Internet/Web Postings
Mass E-mail Solicitation
Departmental/Center Website
Departmental/Center Research Boards
☐ Web-Based Clinical Trial Registries
☒ Clinicaltrials.gov Registry (do not send materials to HIC)

☐ Radio
Telephone
Television
Newspaper

3. **Recruitment Procedures:**
   a. Describe how potential subjects will be identified.

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Potential subjects will be identified through responses to the methods of advertisements listed above. An additional document with the language used for internet/web postings has been included. Furthermore, the research team will reach out to local mental health facilities (including the Connecticut Mental Health Center, the West Haven VA and the Institute of Living) through "lunch and learns", etc. for patient referrals. A lunch and learn is a meeting that research staff schedule with clinicians and therapists at local mental health facilities where an overview of current research protocols are presented and discussed.

b. Describe how potential subjects are contacted.

Subjects will be asked to contact research staff through the advertisement methods listed above. In the event that a subject responds to an advertisement, they will be contacting study staff. In the event that subjects are referred from clinics or mental health facilities, research staff will require that the subjects' clinician contacts the subject first and then refers the subject to the research clinic.

c. Who is recruiting potential subjects?

Members of the research team.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

Please see attached phone screen

HIPAA identifiers:

☒ Names

☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☒ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

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☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.

PI and some co-investigators may provide clinical care to some potential subjects and/or may work in the clinic where some potential subjects are treated.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one: For entire study:_____For recruitment purposes only: __X____

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
NA

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

This data will serve to prescreen subjects who meet obvious exclusion criteria for the study. Thus it avoids subject and investigator burden related to screening of ineligible subjects. Further, due to the stringent I/C criteria, the number of subjects screened who will need to go through exhaustive screening and be exposed to greater risk will increase if all potential subjects are to be brought in for a face to face screening.

iii. Authorization will be obtained prior to subject participation in any research procedure. However, when the subject is initially contacted by phone when referred by a treater or in response to an ad, it would not be feasible to obtain a signed authorization over the phone. Subjects will be notified that all personal health information will remain confidential and will be given the option to be contacted for future research in the event that they are not eligible for the study. **By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.**

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject

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name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - ☒ Compound Consent and Authorization form
   - ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

   Mohini Ranganathan, M.D., Deepak C. D'Souza, M.D., Kim Bielen, B.S., Emma Deaso, B.A., Gina Creatura, B.A., Christina Luddy, B.S.,, Esra Sefik, B.S., Chloe Grond, B.A., Melissa Boucher, B.S., Madison Dykins, B.A., Mackenzie Griffin, B.S., and Ashley Sanders, B.A.

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   The consent process is a multistep process, whereby information about the risks and benefits of the study will be provided to potential subjects across several sessions. The number of sessions over which this information will be provided will depend on how well the subject understands and retains the information. The process begins with the subject initiating contact via telephone. The research staff will provide a brief description of the study following which the subject is screened by a member of the research team. Thereafter, potentially eligible candidates are scheduled for a face-to-face interview. The study procedures will be described as a research tool with potential to enhance our knowledge about the brain. Subjects will also be informed of all potential risks of participation. Subjects will be required to read the informed consent form and the investigator will additionally describe the risks and discomforts.
   To ensure that the study subject understands the study, the subject will be asked questions about the study procedures and the risks associated with participation. If any concern arises that the study subject did not fully understand the study, the principal investigator (PI) may decide that the subject is not suitable for participation. This process generally takes about one hour. If the subject is still interested after all questions have been answered, the PI or staff member consenting, will ask the subject to sign the informed consent form. Any subject who appears incapable of providing informed consent will be excluded. Subjects will be informed that they can decline to participate in the study without penalty and given the opportunity to withdraw from the study prior to analysis of their data. Following the resolution of any questions, the subjects will be asked to sign the consent form if he/she agrees to participate.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

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Great care will be taken to ensure that the subject is able to give informed consent. If any concern arises that the study subject did not fully understand the study, the principal investigator may decide that the subject is not suitable for participation. This process will involve careful explanation of the consent form by a member of the research staff and a post- test to ensure understanding of the procedures and risks of the study. The subject will be required to get 75% of all questions and all the asterisked critical questions correct on a consent questionnaire in order to participate (see attached for details). Parents and family and non-research clinicians will be involved in the process when available. The patient's primary clinician i.e. non-research clinician (if applicable) will be required to assent to patient's participation. This is standard procedure for this clinic with all studies.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

There will be consent forms for all participating subjects. The forms are attached to this application.

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

While we do not plan to actively seek out non-English speaking individuals, we may enroll 1 or 2 Spanish speaking individuals to participate in this study. If the research staff recruits a Spanish speaking subject, an interpreter will be asked to go through the consent form thoroughly with the subject to make sure they have a complete understanding. If the subject is comfortable, they will then be asked to sign the Spanish short form consent form. We will have an interpreter present at all study visits to translate assessments and procedures. In addition, they will meet with a Spanish speaking medical doctor at all safety visits to assess for adverse events and side effects.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒ **Not Requesting a consent waiver**
☐ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☒ No

b. Does a breach of confidentiality constitute the principal risk to subjects?
☒ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☒ Yes ☐ No

☐ **Requesting a waiver of signed consent for the <u>Entire Study</u> (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. <u>Full waiver</u> <u>of consent:</u> (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for <u>Recruitment/Screening</u> only**
a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

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c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Required private identifiable information about individuals will be collected by the research staff and be used for research purposes and charting after consent is obtained. This information includes the results from laboratory tests for both blood and urine, electrocardiogram (ECG) and physical examination results.

b. How will the research data be collected, recorded and stored?

Yale University study team members will collect required research data through study procedures as outlined in this protocol and record it in confidential research records and protected computer files. Data will be stored at the Yale University or the VA in a manner that is compliant with IRB regulations at both institutions.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

All information obtained in this research study will be kept confidential and only be made available to the investigators. In all records of this research study, subjects will be identified by a unique identifier number code known only to researchers working directly on this protocol. These codes will not be derived from subjects PHI (e.g. name, date of birth etc.). A master list of subject names along with unique identifier number will be kept in a locked cabinet in the Principal Investigators office.

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Procedures to ensure confidentiality follow the regulations and policies of Yale School of Medicine. If the results of this research study are reported in any scientific meetings or literature, subjects will not be identified by name or photograph. Records will be maintained according to FDA Good Clinical Practice guidelines to ensure protection of confidentiality and security of

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records. Yale Human Investigations Committee (HIC), who approves the completion of this study at Yale, may inspect study records.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

All protected health information collected specifically for this research will be secured in the manner described above. The data will be stored in a secure location- we anticipate that the data will be stored for at least 10-15 years.

g. If appropriate, has a Certificate of Confidentiality been obtained?
We have obtained a CoC from the Food and Drug Administration.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

If subjects report any threats of violence to a child or elderly person, this will be reported to the Department of Health and Human Services. Threats of violence to self or others will be assessed by the principal investigator who will determine appropriate reporting procedures. Furthermore, positive HIV, hepatitis B, or C results will be reportable to the Connecticut Department of Public Health.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits:
Potential benefits: Subjects will receive no direct benefit from this study. Potential benefits may include improvement in psychotic symptoms, decreased negative symptoms, avoidance of potential side effects from usual anti-psychotic medications themselves or from dose increases of such medications. Overall, the development of novel anti-psychotics will provide benefit to the schizophrenia population as a whole.

Risk/Benefit ratio: As described above, the primary risks of this study are related to CBD administration and are low. Extensive safety measures are in place to ensure that participants with worsening psychosis or mood symptoms are identified expeditiously. The overall risk-benefit ratio is therefore favorable.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

Alternatives include antipsychotics that are currently used to treat psychosis.

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2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Subjects will be paid as below. Subjects will be paid only for the visits that they participate in. Visit payments can be split if procedures for that visit occurred on two separate days, without changing the total payment for that particular visit. Subjects may be compensated up to $25 for unscheduled visits.

Table 1: Payment schedule			
Purpose	Visit	Payment per visit in Period I	Payment per visit in Period II
Screening	Ia and Ib	$25/visit up to $50	N/A
Baseline	II	$75	$75
Week	III	$50	$50
Week	IV	$50	$50
Week	V	$50	$50
Week	VI	$75	$75
Follow up	VII	$25	$25
Compliance	CAROMA	$5/ day up to $80	$5/ day up to $80
	Return of phone	$20	$20
Study close out visit		N/A	$25
Total per period		Up to $475	Up to $450
Total for both periods:		Up to $ 925	

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

Subjects will not be charged for any aspects of this study.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? Yes
   b. Where and from whom may treatment be obtained? Treatment may be provided by the Yale-New Haven Hospital or any health care provider chosen by the study subjects.
   c. Are there any limits to the treatment being provided? Only emergency care

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will be provided. Limits to treatment may be imposed by the insurance carrier of the study subjects.

d. Who will pay for this treatment?

How will the medical treatment be accessed by subjects? The study team will provide assistance to the study subjects in accessing medical treatment through referrals, or the study subject may choose to access treatment on their own. Furthermore, the study team will be in contact with the subject's non-research clinicians who will also aid the subject in getting appropriate treatment.

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Consent Questionnaire

This is a questionnaire to help us to test your understanding of the study protocol. For you to qualify for this study, you will need to pass this test. To pass this test, you will need to score at least a 75% and also get all three questions underlined.

You will have only 2 chances to take this test. Incorrect answers on your first attempt will tell us those parts of the study you did not understand well, so that we can go over the consent form again with you. If you answer more than 5 questions wrong at your first attempt, you will not be considered for this study.

1. Will you need to stop taking your antipsychotic medication as part of this study?

   Yes No Maybe I can decide

2. What medications might you receive?

   Cannabidiol Haldol Placebo Paxil Ativan

3. Will you be able to choose what medication that you may receive in this study?

   Yes No Maybe Don't know

4. During the study, will you or the study doctor or the research team know exactly which study medication you are on?

   Yes No Maybe Don't know

5. Could your schizophrenia symptoms get worse during this study?

   Yes No Maybe Don't know

6. Will blood be drawn for this study?

   Yes No Maybe Don't know

7. Can the study medication have side effects?

   Yes No Maybe Don't know

8. Name at least 2 side effects of the study medication.

   _____ _____

9. Once you start the study, are you free to stop at any time?

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Yes No Maybe Don't know

10. What would happen to your regular treatment if you dropped out of the study?

a. Treatment with regular clinician will end
b. Treatment with regular clinician will continue
c. Don't know

11. Will you be hospitalized for this study?

Yes No Maybe Don't know

12. Will you get paid for taking part in this study?

Yes No Maybe Don't know

_____/ _____

Signature *Date*

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WALLET CARD (CBD)

IMPORTANT

The holder of this card is participating in a clinical study with an investigational drug called ***cannabidiol,*** as a treatment for schizophrenia. There is a 1/2 chance this person can be on placebo.

Treatment Period:

From: _____

To: _____

EMERGENCY CONTACT

If this subject presents to you for treatment, please contact the research clinic below:

Doctor: Mohini Ranganathan, M.D. HIC# 1412015000

Phone: 203-932-5711 x 2546 CBD Study

Doctor: Deepak Cyril D'Souza, M.D. HIC# 1412015000

Phone: 203-932-5711 x 2594 CBD Study

24 Hour Emergency: 203-974-7540

Dial 0 for the operator and ask that the on call research psychiatrist be paged.

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