YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2011-6)

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 two (2) copies 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: Naltrexone for Anti-psychotic Induced Weight Gain in Severe Mental Illness			
Principal Investigator: Cenk Tek, MD		**Yale Academic Appointment:** Associate Professor	
Campus Address: 34 Park Street, 267E New Haven, CT 06519			
Campus Phone: 974-7484	**Fax:** 974-7691	**Pager:** N/A	**E-mail:** cenk.tek@yale.edu
Protocol Correspondent Name & Address (*if different than PI*)**:** Erin Reutenauer Sullivan 34 Park Street, 10 New Haven, CT 06519			
Campus Phone: 974-7317	**Fax:** 974-7691	**E-mail:** erin.sullivan@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*)**: N/A**			
Campus Phone:	**Fax:**	**E-mail:**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:
Does the principal investigator, co-investigator, or any other responsible research team member, or any of their family members (spouse, child, domestic partner) have an incentive or interest, financial or otherwise, that may be viewed as affecting the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? See Disclosures and Management of Personal Interests in Human Research http://www.yale.edu/hrpp/policies/index.html#COI

❑ Yes X No
If yes, list names of the investigator or responsible person:

The Yale University Principal Investigator and all Yale University and Yale New Haven Hospital individuals who are listed as co-investigators on a protocol with a Yale University Principal Investigator must 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 (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Specify Other Yale Location:
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Cancer Data Repository/Tumor Registry

b. External Location[s]:

☐ APT Foundation, Inc.
☒ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Other Locations, Specify:
☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven
☐ International Research Site (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

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.

5 years (2012-2017)

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
☒ 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. Will this study have a billable service as defined by the Billable Service Definition?

Yes ☐ No☒

If you answered "yes", this study will need to be set up in Patient Protocol Manager (PPM) http://medicine.yale.edu/ymg/systems/ppm/index.aspx

7. 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.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1.

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

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.

Advisor Name (PRINT) and Signature _____ 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

SECTION V: RESEARCH PLAN

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

The purpose of this study is to determine the efficacy of two doses of naltrexone (25mg & 50mg) versus placebo for weight and health risk reduction in 200 obese individuals with severe mental illness treated with an antipsychotic medication.

Hypothesis 1: Subjects receiving naltrexone 25mg and 50mg for one year will reduce weight, and improve body mass index (BMI) and waist circumference, at a greater level than the subjects who receive placebo.

Hypothesis 2: Both naltrexone arms will improve health risk markers: serum lipid profile, fasting glucose, and glycosylated hemoglobin (HbA1c) better than placebo.

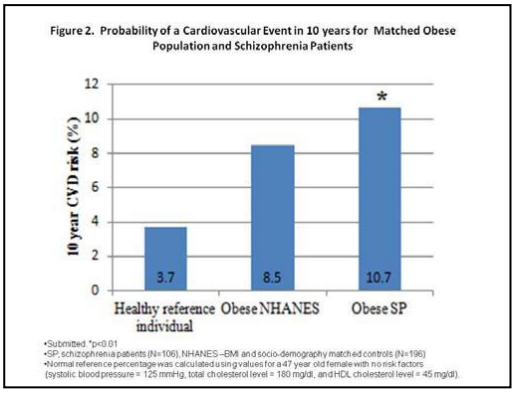
Exploratory Aim: To determine the optimum effective dose of naltrexone to counteract antipsychotic induced weight gain.

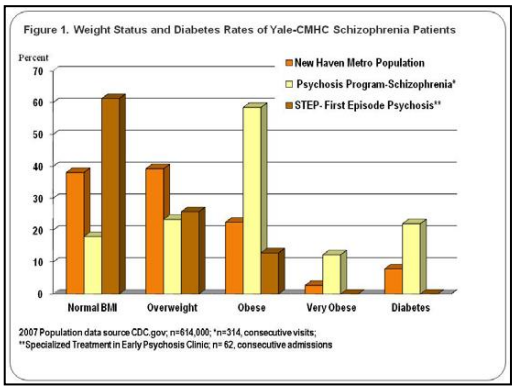
2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Persons with severe mental illness (SMI) die, on average, 25 years earlier than the general population[1-3].Most of this early mortality can be attributed to cardiovascular disease (CVD) and diabetes mellitus (DM), which are directly related to obesity[4,5]. Obesity is a leading cause of preventable death in the United States, second only to smoking. The physical health of patients has become a major focus of schizophrenia care, as recent decades have seen immense gains in symptom control and community integration. There is an urgent need for the development of interventions that address the obesity crisis in schizophrenia[6].

Obesity rates in psychiatric populations are much higher than the general population. Several studies demonstrate an alarming increased prevalence of obesity among patients with SMI. Allison et. al. found that 42% of a group of individuals with schizophrenia had a BMI of 27 or greater, compared to 27% of the general population[7]. In the Northern Finland 1966 birth cohort study, rates of obesity in patients with schizophrenia were 42% compared to 13% for rest of the cohort. Keck et. al. reviewed 45 studies of patients with bipolar disorder and found that the overall prevalence of overweight and obesity was higher in these patients than in control populations[5]. Studies of obesity risk need to carefully examine socioeconomic and geographic differences. Figure 1 shows our (unpublished) analysis of obesity and DM rates in a large schizophrenia cohort, compared with a socioeconomically- and geographically-matched

population sample. Both obesity and DM rates are about three times higher among patients with long standing schizophrenia than the general population. Obesity is associated with significantly increased outpatient medical costs (25%)[8-9]. Both SMI and obesity are associated with significant stigma, and discrimination at work or in society[10,11]. Obesity in SMI has been associated with additional decline in quality of life[12] and improvement has been shown with weight loss[13,14]. We have recently completed an analysis comparing cardiovascular risk of obese schizophrenia patients to similarly obese matched population controls (submitted). It appears that not only do schizophrenia patients suffer from higher rates of obesity, but the impact of obesity is also more dramatic. Obese individuals with schizophrenia had a mean vascular age that was 14.1 years older than their mean actual age compared to a 6.7 year difference for socio-demographic and BMI matched population controls; these obese patients also had significantly higher cardiovascular event risk (Figure 2). This finding underscores the higher impact of obesity, and urgency of the problem in this vulnerable population. ***Increased obesity rates in schizophrenia is an iatrogenic problem.*** Fig. 1 also depicts our first episode psychosis cohort, which did not have increased rates of obesity, or diabetes at the onset of their schizophrenia treatment. Indeed, we have shown that the age adjusted cardiovascular risk for first episode patients is similar to population controls during initial assessment [15]. On the other hand, after one year of treatment, mean BMI increased by 9% in first episode schizophrenia patients (n=79) vs. 1% in age matched population controls (N=156). During this period, Framingham 10 year CV risk score disproportionately and significantly increased from 0.7 to 1.22 for first episode patients, whereas it remained similar (0.74 to 0.79) in population controls). Both results were highly significant (manuscript in preparation). These findings from our group provide preliminary evidence that obesity is not a direct result of schizophrenia. Indeed, several lines of evidence support this notion. First, pre-antipsychotic era historical data typically points to lower than population average body weight, even after the development of specialized nutrition programs to bring patients up to population weight norms[16,17]. Second, historical data also suggest normal fasting sugar and oral glucose tolerance tests among schizophrenia patients[18]. Third, untreated chronic schizophrenia patients, as can be found and studied in India, appear to have lower body weight and metabolic profiles that are similar to those of historical cohorts[19]. Fourth, first reports of excessive increases in body weight initially appeared following the introduction of first-generation antipsychotic medications[20,21]. Combined with the short and long term weight gain observed with antipsychotic use in various patient groups, the evidence indicates that increased obesity in schizophrenia is largely an iatrogenic problem[22]. In ours and other's analyses of risk factors for obesity, it is clear that obesity rates are closely associated with the appetite-increasing side effects of antipsychotic medications[23]. Patients on antipsychotic medications consume more total fat and sugar than comparable populations (in press)[23]. They also perform significantly less moderate physical activity, and have less nutritional knowledge than matched general population samples (in press).





Antipsychotics significantly contribute to the increased rates of obesity, and related medical

morbidity. Anti-psychotic medications have been associated with weight gain since their introduction in the 1950's[22]. In a landmark study, Allison et al reviewed available research data and found that patients on average gain weight after 10 weeks of treatment with any antipsychotic medication, but that there were differences across medications: patients taking clozapine had a mean weight gain of 3.99 kg, followed by a mean weight gain of 3.51 kg for olanzapine treated patients, 2.10 kg for chlorpromazine, 2.00 kg for risperidone, 0.48 kg for haloperidol, 0.43 kg for fluphenazine, and 0.04 kg for ziprasidone[22]. Results from a different study reported mean weight gains of 0.71 kg for Aripiprazole and 2 kg for quetiapine [6]. In the CATIE trial, >7% of baseline weight gain occurred in 30% of patients taking olanzapine over 18 months, but only 7% to 16% of patients taking other antipsychotics had this clinically significant weight gain [24]. Although some agents appear to have better weight gain profiles than others in the above mentioned studies, these results are somewhat misleading, since the data is obtained from patients already taking antipsychotics. Even aripiprazole and ziprasidone, with their more favorable weight gain profiles, produce over 7% total body weight gain in approximately 10% of clinical trial subjects (PDR). In a large study of first episode psychosis patients, participants gained an average of 16 kg on olanzapine and 7.5 kg on haloperidol[25]. Figure 3 presents weight gain observed with various antipsychotic agents published from first episode psychosis studies. Both first generation agents, as well as second generation agents with seemingly more favorable weight gain profiles, produced significant weight gain for these relatively young and more active patients. The mechanism of weight gain associated with the novel antipsychotics has not been fully elucidated, but may be related to blockade of histamine (H1), serotonin 2C (5HT2c) and alpha 1- adrenergic receptors on hypothalamic neurons, resulting in distortion of signals from the gastrointestinal tract to the brain. Such distortion may in turn lead to excessive appetite and impaired satiety signals[26,27]. H1 receptor blockade is well known to increase appetite, and affinity for this receptor is clearly the best predictor of weight gain liability[28]. Similarly, 5HT2c receptors play a role in energy regulation, and agonism of this receptor reduces appetite and weight[28,29]. While these two receptors may explain the excess weight gain that is observed with newer agents, they fail to explain the weight gain produced by agents, like haloperidol, which have no affinity to these receptors. In fact, the sole effect of haloperidol is to block D2 receptors, an action which is shared to a varying degree by all approved antipsychotic agents. Thus, D2 receptor blockade appears to play an additional role in weight gain. D2 receptors are not directly involved with energy regulation; however, they do play an important role in the brain's food reward system. Food is one of the primary substrates of the reward system in higher living organisms. Highly storable energy sources, such as fats and sugars, are extremely enjoyable through the actions of opiate receptors, which are partly mediated by D2 receptors[30]. Blockade of D2 receptors may make the whole system less sensitive to stimuli, and thereby push the organism to eat more in order to achieve similar levels of enjoyment.

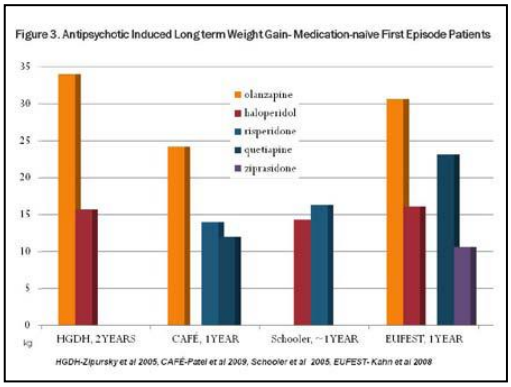


Table 1. Summary of Prospective Behavioral Weight Management Studies for Psychotic Outpatients				
	Intervention N	**Intervention weight change (weighted mean)**	**Control N**	**Control weight change (weighted mean)**
Prevention of weight gain (RCT)	79	**+2.1kg**	76	**+7.1kg**

Weight loss (RCT)	141	**-2.7kg**	121	**+0.4kg**
All Published	544	**- 2.0kg**	217	**+ 2.7kg**

Behavioral interventions for antipsychotic induced weight gain are necessary but not sufficient.
There have been several non-randomized, prospective, clinical intervention trials[31-45] using a variety of behavioral methods for obesity management in patients with SMI; these methods include nutritional education, commercial programs and lifestyle interventions. These studies can be categorized into two classes: those aimed at preventing weight gain and those aimed at promoting weight loss. These studies are small and heterogeneous, but for the sake of brevity, in Table 1, we summarize the results for the 15 studies that have been published to date[31-45]. Regardless of the method used, most studies arrested weight gain, and/or provided modest weight reductions (Table 1). Only 6 of these trials were randomized, controlled studies (RCT) of weight loss for obese patients with schizophrenia, 3 of these studies used lifestyle modification[32,37,45], and 3 studies utilized CBT[31,31,38]. The weighted average reported in these studies for intervention groups is 2.7 kg weight loss (range 2.0-4.0 kg) over an average intervention of 15 weeks compared to a 0.4 kg weight gain for control groups. As can be seen in Table 1, behavioral weight loss programs provided limited benefit for patients with schizophrenia, especially compared to the long term weight gain produced by antipsychotics.

Preliminary Study: SIMPLE Weight Loss Program (Simplified Intervention to Modify Physical activity, Lifestyle, and Eating behavior):

We have recently completed the largest randomized weight loss trial in schizophrenia patients using our SIMPLE program. This is an intensive 16 week lifestyle intervention that adjusts for the cognitive impairment of schizophrenia, integrates social cognitive theory, and utilizes other components of successful lifestyle programs. First, the concepts and language implemented in the program are simplified, the information is imparted at a slow pace initially then builds progressively, and knowledge is reinforced with repetition. This simplified approach is crucial for retaining study subjects because lower perceived rule complexity is associated with lower attrition. Second, we used an innovative food reimbursement program. This program provides financial reimbursement for healthy foods purchased. The reimbursement is not contingent on weight loss; instead, it serves as a behavioral reinforcement and learning tool. Financial reimbursement addresses the disparity in income, since the higher cost of healthy foods represents a barrier to dietary change for low SES individuals. Lastly, our intervention includes supermarket visits to teach how to shop for healthy foods while on a budget and how to negotiate large, crowded stores. This trip also reinforces nutrition label reading. Additionally, participants are given bus tokens and given guidance about which markets to shop at.

Pharmacological weight loss interventions: **First**, the obesity problem in schizophrenia is not purely behavioral, given the substantial contribution of antipsychotic medications. As seen in our large RCT, patients are able to implement lifestyle changes, arrest weight gain, and improve serum risk markers; however, these gains are limited. Greater weight loss might be achieved by simply stopping the antipsychotic medication; many patients do, and the results of stopping medication can be catastrophic. **Second**, persons with schizophrenia often have significant attention and learning problems, which complicates the delivery of behavioral programs to this population more than the general population. Even in a specialized program, such as SIMPLE, these obstacles may not be completely offset. **Finally**, there is limited support by health care systems and funding agencies for implementing behavioral programs to treat obesity because the magnitude of weight loss achieved in clinical studies is one sixth to one-third of the average weight gain induced by antipsychotic medication.

Opiate antagonists may be useful for antipsychotic induced weight gain:

Reward system, opioid receptors and appetite: The biology of feeding and regulating body weight is extremely complicated, not exactly elucidated, and a full presentation is beyond the scope of this application. Many neuropeptides, hormones, and neurotransmitters, both in the brain and the GI tract,

are involved. Like any non-automatic function that is essential for survival, mammalian feeding behavior is closely modulated by the reward circuits in the brain. Endogenous opioids play an important role in these reward circuits[46]. Opioid derivatives have been used in human medicine for more than a millennium, and their appetite increasing effects are well known. Following the discovery of endogenous opioids, it was discovered that opioid receptor antagonists (ORA) decrease self-feeding in food deprived rats[47]. Since then, the animal literature has expanded significantly, and this finding has been replicated in non-food deprived rats and many other mammalian species (reviewed by Bodnar[47]). It is now fairly clear that ORAs have little effect on initiation of feeding, but rather attenuates preference for "palatable diets" and eating behavior[48]. Injecting animals with opioids increases the preference for high carbohydrate, and even more so, on high fat diets, an effect readily blocked by ORAs. There is no evidence that ORAs actually block the taste sensation in animals or humans[47]. Human studies revealed intact taste, but a decrease in the pleasantness of sweets, after administering the ORA naltrexone[46]. Since ORAs block the preference for saccharin solutions in rats, it appears that the macronutrient or caloric content of food does not activate opioid pathways [49].

Dopamine connection: Other findings show that palatable foods result in endogenous opiate release, related mRNA expression, and opioid receptor occupation in sites of the brain that are critical for both feeding and overall reward circuits, most strikingly in nucleus accumbens and hypothalamus[46]. Rewarding effects of opioids are exerted mainly through dopamine41. Obese human subjects are shown to have significant increases in their circulating β-endorphin levels than non-obese controls[82]. Also, more palatable foods are shown to induce higher circulating β-endorphin levels in normal weight human subjects[83]. Increased extracellular dopamine levels occur in the nucleus accumbens and striatum in response to rewarding food stimuli. Of note, obese subjects have been shown to have lower striatal D2 receptor availability, at a rate that is inversely proportional to the level of obesity. A mechanism for obesity in this population has been proposed in which overeating occurs in an attempt to stimulate the dopamine system.

A working hypothesis of antipsychotic induced weight gain: Patients with schizophrenia treated using antipsychotic medications have been shown to have a preference for diets high in fat and sugar. Patients with schizophrenia typically seek behaviors that increase dopamine mediated reward in the brain such as smoking and substance use, both of which occur more often in this group than the general population. The system might require intact dopamine and opioid function. We propose a model where patients with schizophrenia increase their intake of foods high in sugar and fat in order to increase their low dopaminergic tone,which results from dopamine receptor blockade, via endogenous opioid release. The finding that medicated obese women with schizophrenia have been shown to possess higher circulating β-endorphin levels than matched controls provides partial support for this hypothesis[52]. Medications with additional H1 receptor blockage impair satiety signaling from GI tract to the hypothalamus; thus, there is no "stop" signal to reward eating, which in turn causes further weight gain.

Clinical trials with the opioid receptor antagonist naltrexone for obesity:

Naltrexone is an oral agent that competitively antagonizes all known opioid receptors in the brain. Human studies with naltrexone were completed in individuals with different illnesses, including schizophrenia, and have been shown to be a safe and easy agent to use. It is shown to decrease craving in alcoholics and is approved by the FDA for the treatment of alcohol dependence[53]. Naltrexone is reported to decrease craving for other substances of abuse, like nicotine. Furthermore, it has been shown to prevent secondary weight gain due to cessation of cigarette smoking at low (25mg and 50 mg), but not higher doses[54]. Naltrexone has been tested in human feeding studies, and has been shown to reduce both the quantity of food eaten and the choice of palatable foods[46]. A study that was conducted for antidepressant- and lithium-induced weight gain in bipolar women reported weight loss during naltrexone treatment; however, weight on average returned to baseline after cessation of active

treatment. Patients reported decrease in food cravings while they received naltrexone, but not while taking placebo in this study[55]. There is also a well studied bupropion/naltrexone combination currently in FDA review for obesity treatment. Only one of these large studies provided lifestyle intervention to both groups: the placebo group lost 5.1% of TBW and the active group lost 9.3% over a 56 week period[56]. Although, the kg difference between the two groups is not published, we calculated it as about 4kg from the information provided in the paper. In another study by the same company, naltrexone alone at a 48mg dose provided 1.2 kg (1.7kg completers) average weight loss over 24 weeks, which was slightly better than placebo (0.8kg), but only half of the bupropion/naltrexone combination (about 5kg at all doses)[57]. The rationale for combining bupropion/naltrexone is based on the anorexia reported with both medications. While admitting possible effect through mesolimbic dopamine reward pathways, the investigators speculate that the actual effect is due to bupropion blocking dopamine reuptake, which results in increased α-melanocyte stimulatinghormone (MSH) levels leading to decreased appetite. β-endorphin in turn produces feedback inhibition for MSH secretion. Thus, by blocking naltrexone's feedback inhibition, they believe the bupropion effect is enhanced. This hypothesis provides a related but separate pathway on why naltrexone may be useful for antipsychotic induced weight gain. Since MSH release is possibly mediated by D2 and D1 receptors which are partially blocked by antipsychotic use, the MSH release may be decreased and further inhibited by high β-endorphin levels due to overeating. In this case, the addition of bupropion would not be useful, but naltrexone might block the feedback inhibition and reduce appetite through MSH activity. Among several bupropion studies for smoking cessation in schizophrenia concomitant to antipsychotic use, only one –from our center reported weight effects. In this study, both bupropion and placebo groups gained similar levels of weight regardless of their quit status[58].

PROOF OF CONCEPT: Pilot Study of Low Dose Naltrexone To Arrest and Reduce Antipsychotic Induced Weight Gain (clinicaltrials.gov identifier NCT00793780):

Based on our working hypothesis that opioid receptor blockade might arrest antipsychotic induced weight gain, we have conducted a pilot 8 week randomized, double blind, placebo controlled, parallel, fixed dose clinical study of naltrexone (25mg) for treatment of weight gain in schizophrenia. The study was supported by Women's Health Research at Yale and only obese women with clinically stable schizophrenia who had gained over 2% of their TBW in the previous year were recruited. Substance abuse and pregnancy were the major exclusion criteria. Over a period of one year, 29 volunteers were screened, and 24 subjects were randomized to 25 mg oral naltrexone or matching placebo for a period of 8 weeks. No diet advice or behavioral weight loss intervention was provided. No subjects reported joining an outside program at the end of the study. One subject in the placebo arm dropped out at the fourth week due to personal reasons, all remaining subjects completed the 8 week trial. No serious adverse effects were reported and study medicines were well tolerated. At the end of the study, subjects who were randomized to active naltrexone arrested the weight gain, with a further average reduction of 2.45 kg as opposed to subjects who were randomized to placebo, who continued to gain weight at an average of 0.47kg (Figure 3). The difference between two groups closely approached significance at p=0.051, and produced a power of d=0.59. Baseline weight was not correlated with weight change in the study. On the other hand, exploratory analyses revealed that diabetes was a confounding factor, and only non-diabetic subjects on naltrexone lost significant weight compared to placebo subjects (non-DM **-4.98kg** (±3.03) vs. DM - .27 (±3.05),Figure 3). It was also discovered that the intensity of craving for sweets as measured by the Questionnaire of Cravings for Sweet and Rich Foods (QCSRF) was significantly reduced for the NTX group and unchanged for the placebo. Unfortunately the study was underpowered, as expected from a pilot study, and provides no information on naltrexone effects on males. In spite of these limitations, our study provides important information. Given that obese patients with chronic schizophrenia typically continue to gain weight at a clinically significant level, this pilot is unique among other studies, and its results must be interpreted within this

clinical context. The current study will focus on non-diabetics which constitutes about 80% of the SMI population[59].

RATIONALE AND SIGNIFICANCE: In summary, obesity interventions in severe mental illness are urgently needed. Unfortunately, behavioral programs are not sufficient to counter the antipsychotic induced weight gain due to the magnitude of the problem and the ongoing need for antipsychotic medications in schizophrenia. Pharmacological strategies to augment the behavioral programs need to be developed. Currently available medications for this purpose are limited and have not been effective in this population. Antipsychotic medication actions on H1 and 5HT2 receptors only partly explain why they cause weight gain. We developed a working hypothesis that D2 receptor blockade might be partly responsible for weight gain by interacting with the dopamine-opioid system. In a proof of concept study, we have shown that an already FDA approved, widely available, and inexpensive generic oral opioid antagonist, naltrexone, was able to arrest antipsychotic induced weight gain and provide significant weight loss in a relatively short time period. FDA obesity intervention guidelines necessitate adequately powered, longer duration studies. Thus, in this application we are proposing a fully powered, randomized, double blind, placebo controlled study of two different doses of naltrexone for adequate duration to counteract antipsychotic induced weight gain.

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3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths.

Subjects will be randomized to active Naltrexone 25mg, Naltrexone 50mg, and placebo groups in a 1:1:1 ratio using a computer randomization procedure at the CMHC research pharmacy, blind to both research team and subjects. Separate randomization schedules will be applied based on gender, and antipsychotic agent to yield an equal number of male and female subjects in each arm. This is to control for possible differential gender and racial/ethnicity specific effects of Naltrexone on weight as well as differences brought on by higher and lower weight liability medications.

Subjects will take the study medication daily for 52 weeks. Subjects will be seen weekly for the first 4 weeks of the study, thereafter they will be seen on a bi-weekly (every other week) basis to be assessed (i.e. weight, side effect check, paper questionnaires) throughout the remaining 48 weeks of treatment. Compliance will be monitored by pill counts as well as 25mg riboflavin added to the capsules which provides florescence to urine under Wood's lamp (UV or black light). Subjects will be given a study identification card listing the fact that they may be taking naltrexone and this card will include the study emergency cell phone number which will be available 24 hours a day, 7 days per week in case of an emergency.

The study is planned to be run at the Connecticut Mental Health Center (CMHC) and its affiliated satellite clinics throughout the greater New Haven area.

All participants will be carefully assessed with physical examination and laboratory findings, any medical problems that need immediate attention will be referred to each participant's own primary care physician. All potential subjects will meet with study staff for intake and evaluation sessions to determine eligibility prior to enrollment.

A description of assessments is given below:
1) Intake interview including demographics, clinical history, Structured Clinical Interview for DSM-IV (**SCID**) to ascertain diagnosis. 2) Urine toxicology (**Utox**) screen to rule out substance use. The initial sample will also be sent to the lab to confirm opiate results for safety purposes and a follow-up sample will be taken immediately before randomization to study medication to ensure it is negative for opiates; continued random testing will occur at the discretion of the study physician throughout the trial along

with medication compliance procedures; and pregnancy tests for female subjects as it may not be advisable for pregnant women to lose weight. 3) Weight (**Wt**) measurement to the nearest 0.5kg and height (**ht**) will be measured to calculate **BMI**. Waist circumference (**WC**) will be measured with a tape measure placed on the midpoint between iliac crest and lowest rib rounded to the nearest 5 mm. Resting blood pressure (**bp**) and pulse will be measured. Our lab has established procedures for calibrating scales (National institutes of Standards and Technology Certified weights) and waist measurement. The lab conducts reliability exercises for waist measurements for study stuff (ICC= 0.97, TEM=2.4%) 4) Standard Laboratory Testing (**Lab**) 5) Brief Psychiatric Rating Scale (**BPRS**) is the gold-standard overall measure of schizophrenia symptoms which will be utilized to demonstrate that the Naltrexone and/or SIMPLE intervention does not cause worsening of the illness symptoms apart from the usual fluctuations of the natural course. 6) Beck Depression Inventory (**BDI**) 21-item version is a psychometrically sound, widely used measure of the features and symptoms of depression. The BDI taps a broad range of negative affect – not just depression – and is a highly efficient measure for detecting fluctuations in broad psychopathology and distress. 7) Three Factor Eating Questionnaire (**TFEQ**) also known as the Eating Inventory is a measure of eating behaviors with three factors: dietary (cognitive) restraint, disinhibition, and hunger. The TFEQ has received psychometric support and is a frequently used measure in obesity trials. 8) The Questionnaire on Craving for Sweet or Rich Foods (**QCSRF)** The QCSRF is a two factor, nine item scale assessing the presence of cravings for rich and sweet foods and has been found to have good psychometric properties. 10) The Yale Physical Activity Survey (**YPAS**) is an interview-administered questionnaire that assesses activity participation in number of hours/week in different categories (i.e. work, recreation, exercise) and takes about 20 minutes to complete. 11) Resting Metabolic Rate (**RMR**) is calculated through a mathematical formula not indirect calorimetry. No special procedure is utilized that would be bothersome to subjects. 12) Quality of Life Enjoyment and Satisfaction Questionnaire (**Q-LES-Q**) is specifically designed to use with schizophrenia patients and focuses on patient's subjective perception of various aspects of their life. 13) SF-36 Health related Quality of Life Questionnaire; a 36-item short-form (**SF-36**) was constructed to survey health status in the Medical Outcomes Study. The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale that assesses eight health concepts: 1. limitations in physical activities because of health problems; 2. limitations in social activities because of physical or emotional problems; 3. limitations in usual role activities because of physical health problems; 4. bodily pain; 5. general mental health (psychological distress and wellbeing); 6. limitations in usual role activities because of emotional problems; 7. vitality (energy and fatigue); and 8. general health perceptions. SF-36 can be administered as a self-rating scale or by interviewer. In this study, trained rates will administer the SF-36. 14) UKU Side Effect Checklist (**UKU**) This is a comprehensive rating scale developed for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Common adverse events related to naltrexone will be added to this scale, as needed. 15) Columbia-Suicide Severity Rating Scale **(C-SSRS126)** is a scale developed for use in clinical trials of psychoactive agents and recommended by the FDA to be used for safety tracking of medications for suicidality. 16) Cognitive Battery. Tests from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (**MATRICS**) Consensus Cognitive Battery (**MCCB**): Given the cognitive impairment of schizophrenia, careful assessment of cognition is necessary for feasibility of any medication use in schizophrenia. This is a cognitive battery developed on NIMH initiative by experts from academia, pharmaceutical industry, and US government for the specific purpose of use in clinical trials in schizophrenia. Validity, reliability, sensitivity to change, and normative data is established.

4. **Genetic Testing N/A** ☒
   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
      ii. the plan for the collection of material or the conditions under which material will be received

Assessment Schedule

SCID, Demographics, Physical exam	Week 0
Urine toxicology, pregnancy test for female subjects	Week 0 and every 4 weeks subsequently + as needed
Fluorescence check in urine for compliance	determined by study physician
Fasting Glucose, Insulin, HbA1c, Lipid Profile, Liver function tests	Week 0, 16, 32, 52
Serum leptin, ghrelin, peptide YY, adiponectin, high sensitivity CRP, interleukin 6	Week 0, 16, 52
Framingham Score	Calculated same time with blood draws.
Vitals (Blood Pressure, pulse)	Weekly for first 4 weeks, then every two weeks
Weight, BMI	Weekly for first 4 weeks, then every two weeks
RMR, Waist Circumference (WC), 24hr Food Recall, TFEQ, YPAS, BPRS, BDI, QCSRF, QLS, SF-36, **C-SSRS.**	Week 0 and every 4 weeks
UKU side effects	Weekly for first 4 weeks, then every two weeks
Cognitive Battery	Week 0, Week 16, Week 52

      iii. the types of information about the donor/individual contributors that will be entered into a database
      iv. the methods to uphold confidentiality

   B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
   C. Is widespread sharing of materials planned?
   D. When and under what conditions will materials be stripped of all identifiers?
   E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
      i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

   F. Describe the provisions for protection of participant privacy
   G. Describe the methods for the security of storage and sharing of materials

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

200 patients with severe mental illness

6. **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)

Subjects must pass the following quiz (80% correct) in order to be eligible to consent for the study.

1. I will take study medication for 52 weeks/1 year in this study. T_X_ F____
2. This study aims to help me lose weight. T_X_ F ____
3. I have to be in the study, even if I don't want to. T____ F _X_
4. I will have blood drawn in this study. T_X_ F ____
5. I should report to the study doctor if I have any side effects T_X_ F ____
6. I will be paid for study assessments. T_X_ F ____
7. The study doctor and research team will know which medication I'm taking during the study. T____ F _X_
8. Please circle the names of the study medication that you may receive in this study.

   Haldol Prolixin Mellaril

   Naltrexone Paxil Placebo

9. I can stop being in the study any time that I want. T_X_ F ____
10. One of the possible side effects of the study medication in nausea. T_X_ F____
11. If I take the study medication while taking an opiate (see list on last page) I may experience withdrawal symptoms, such as nausea, vomiting diarrhea, muscle aches, abdominal cramping, anxiety, and sweating. T_X___ F ____

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

Inclusion Criteria

1) Age 18 to 75
2) Meet DSM-IV criteria for schizophrenia, schizoaffective disorder, bipolar disorder, major depression, or another psychotic disorder based on SCID interview
3) Body Mass Index (BMI) of 28 and over
4) On a stable dose of antipsychotic medication; i.e. at least one month with no dose change, and three months from an antipsychotic switch
5) Deemed to be symptomatically stable by the clinical staff in the last two months

6) Over 7% total body weight increase on antipsychotics for subjects within first year of illness

Exclusion Criteria

1) Meet criteria for current opiate abuse or dependence (confirmed by positive urine drug screen for opiates or, if suspected by study doctor via patient history and or suspicion of occult opiate use, a naloxone challenge will be performed.)
2) Current history of dementia, mental retardation
3) Not capable of giving informed consent for participation in the study
4) Women who are pregnant or breast-feeding
5) Physical conditions affecting body weight (e.g. Cushing's disease, polycystic ovary syndrome)
6) Diabetes Mellitus (defined as prescribed an anti-diabetic medication for diabetes or a hemoglobin A1c level > 7 confirmed by primary care physician at screening)
7) Severe liver dysfunction, (serum aminotransferases greater than three times normal), acute infectious hepatitis, liver failure.

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

Eligibility will be determined through participant report, chart review, and communication with CMHC clinician/psychiatrist, and this will be completed by the PI and research coordinator.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Naltrexone 25mg/50mg/Placebo

Hepatotoxicity: Liver functions reported to be effected in terms of increased liver transaminase levels at doses of naltrexone 10 to12 times the study dose. No hepatotoxicity reported at or twice the study dose.

Opioid Withdrawal: Naltrexone may cause acute withdrawal on subjects who had used opioids as far as seven days before the drug administration. Symptoms commonly associated with opiate withdrawal include severe nausea, abdominal cramping, diarrhea, vomiting, muscle aches, anxiety, and sweating.

Reduced efficacy of opioid medications with naltrexone: Patients taking naltrexone may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. In an emergency situation when opioid analgesia must be administered to a patient taking naltrexone, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. Study participants will carry an information card to be used in case of an emergency.

Small increased risk of depression, suicidal ideation, and suicide: Based on data from placebo controlled trials in patients with alcohol and/or opiate dependence there was observed an infrequent however small increased incidence of depression, suicidal ideation, attempts, and completed suicides in the naltrexone treated group compared to the placebo group.

Other Side Effects: In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Exposure to Naltrexone during Pregnancy: Naltrexone is a pregnancy Category C medication meaning the drug should be given to patients only if the potential benefit justifies the potential risk to the fetus. There is no data on the use of naltrexone or other opioid antagonists in pregnant women. The effects, if any, on the developing fetus are unknown. We will require that female patients of child bearing age use contraception to prevent pregnancy during participation in the study and will not enroll participants who are pregnant or who are trying to get pregnant.

Urine collection
Urine specimens are collected for research assessments and should pose no appreciable risks, and will be done using established procedures already in place at CMHC.

Blood collection
Subjects participating in these studies will have multiple blood draws using established procedures in the CMHC. The blood draw has the risk of producing a bruise at the venipuncture site, and rarely development of a small infection.

Cognitive Assessments, Rating Scales and Questionnaires
These are all non-invasive, should add no risk, and have been used without difficulty in previous studies with these populations. The disadvantage is that they are time consuming to complete. Our experience in the past with these measures is that they are acceptable to subjects, and careful efforts will be made to ensure confidentiality of this data, including coding of the research assessments by study subject numbers, which are kept in locking filing cabinets or in password protected computers, with access only to key research staff.

Suicide Risk
Due to the small increased incidence of depression, suicidal ideation, attempts, and completed suicides in people having taken Naltrexone, we will monitor this risk using the Columbia Suicide Severity Rating Scale. If, during screening or throughout the trial, a patient indicated suicidal thoughts or plans, they will be further assessed by a clinical team member or the study doctor, who will then refer the patient to their regular clinician, CMHC acute services or the YNHH emergency room, as indicated.

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

Described above

11. **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? N/A
    c. Data Safety Monitoring Plan

This is a moderate risk study. Although the naltrexone dosages we use are at and below the FDA approved dose and this drug has been safely used in this particular population in the literature, the

potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows.

The principal investigator is responsible for monitoring the data, assuring protocol compliance. The safety officer is responsible for conducting the safety reviews bi-annually. During the review process, the safety officer will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, the safety officer, the Human Investigation Committee (HIC) or Human Subjects Committee (HSC) have the authority to stop or suspend the study or require modifications.

This protocol presents moderate risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the HIC or HSC (using the appropriate forms from the website) and any appropriate funding and regulatory agencies (NIH). The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project In accordance with Federal and Institutional regulations, the Data and Safety Monitoring Board (DSMB) for this study will conduct bi-annual reviews of aggregated study outcome data and adverse events via a set of tables updated by the study coordinator, per our DSMP with NIH. The chairman of the DSMB and designated safety officer will be Dr. Eda Cengiz, Assistant Professor of Pediatric Endocrinology. The DSMB committee will be composed of Tyrone Cannon, Ph.D., a Professor of Psychology and a foremost leader in the field of clinical neuroscience. His work focuses on schizophrenia and related disorders, in particular on identifying the neurocognitive, neuroanatomical, and neurochemical changes associated with genetic liability to schizophrenia; Bingqing (Teresa) Zhou, Ph.D. an Assistant Professor in the departments of Biostatistics and Public Health. Her current work involves regression modeling and focuses on design and analysis of clinical trials; and James I Hudson, M.D., Sc.D., a professor of Psychiatry at Harvard Medical School. He also serves as the director of the Biological Psychiatry Laboratory and the director of the Psychiatric Epidemiology Research Program at McLean Hospital. The committee will be presented aggregated data on study outcomes and adverse events on a bi-annual basis in a blinded manner.

Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures/design by the principal investigator according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE.

Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the HIC or HSC:

The investigator will report the following types of adverse events to the HIC(IRB), DSMB and the FDA (as appropriate): a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others. These adverse events or unanticipated problems involving risks to subjects or others will be reported to the HIC (IRB), DSMB and the FDA (as appropriate) within 48 hours of it becoming known to the investigator, using the appropriate forms found on the website.

We plan to report adverse events to co-investigators on the study, DSMB members (listed above), funding and regulatory agencies and regulatory and decision-making bodies. Specifically, for the current study: National Institutes of Health (NIH)/National Institutes of Mental Health (NIMH).

The safety officer (Eda Cengiz M.D.) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and

severity of the adverse events and determine if modifications to the protocol or consent form are required at that time.

The Safety officer will be completely independent of the DSMB and information will be provided to the DSMB in the form of tables, narrative summaries etc. Data on the potential side effects of Naltrexone will also be reported to the DSMB members via these tables. The study coordinator will provide these tables etc as blinded data reports to the DSMB on a bi-annual basis.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
   ii. What provisions are in place for management of interim results?
   iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Data will be electronically scanned into databases and will be double checked by hand. Hard copy documents will be examined to verify questionable observations. Missing data will be examined for each variable. Histograms, normal probability plots, and numerical summaries (skewness, kurtosis) will be used to examine distributional assumptions required for the mixed model analysis described below. Transformations such as the logarithm, square root, and reciprocal will be considered in the event the normality assumption is inadequate. Residual analysis will also be performed to evaluate distributional variance and linearity assumptions. Data analysis will be conducted in collaboration with Brian Pittman, statistician in the department of Psychiatry and Dr. Ralitza Gueorguieva faculty member of the Department of Biostatistics at Yale University School of Public Health. For all analyses, an alpha threshold of 5% (two-sided) will be used to test for statistical significance and will be performed using SAS v9.3 (SAS Institute, Cary, NC).

Analyses will be performed according to the intent-to-treat (ITT) principle where data from any randomized subjects will be analyzed. We will calculate descriptive statistics for participants at baseline, and compare naltrexone to placebo participants using analysis of variance (ANOVA) for normally distributed covariates and chi-square tests for categorical covariates. The impact of baseline variables that demonstrate clinically relevant group differences will be assessed in supportive analyses using covariate adjustment.

Approach to Missing Data: The primary analysis method will use a likelihood-based mixed model, which accommodates incomplete observations and operates under the assumption that the missing data is missing at random (MAR). Missing data patterns, time to withdrawal and reasons for dropout will be compared between the two naltrexone and placebo groups. T-tests, cross-tabulations, and logistic regression will be used to evaluate whether withdrawal is dependent on any observed variables. Finally, should missing data patterns and reasons for missing data suggest a bias or confounding, we will conduct sensitivity analyses using pattern mixture models to examine the influence that dropout bias (informative missingness) may have on treatment differences. Multiple imputation (MI) will also be used in the case of data not MAR. Sensitvity analyses will be performed secondarily among study completers.

Hypothesis Testing: The primary goal of this study is to compare the weight changes resulting from two different doses of naltrexone compared to placebo. The primary ITTanalysis will employ a linear mixed effects model (LMM) to determine the effect of treatment status (between-subjects for: naltrexone 25/50mg vs. placebo) on the trajectory of weight change over time (within-subjects for: study time points). The interaction between treatment and time will be modeled and interpreted using graphical displays and post-hoc contrasts on least square means. The latter will include estimation of group contrasts at each time point and polynomial (linear, etc.) contrasts for time within each group. However, the primary contrasts will be each dose compared with control at 52 weeks. Because the outcome data are correlated (i.e., weight assessed from the same subject at different time points), weight over time will be modeled through the inclusion of random subject effects and/or structured variance-covariance matrices, with the best-fitting structure determined by Bayesian-Schwartz Information criteria (BIC). Supportive analyses will also include covariate adjustment for clinically significant variables (as determined from baseline evaluations and also other treatment variables, such as sessions attended). The above model will be fit using SAS PROC MIXED (Cary, NC), using restricted maximum likelihood (REML). The effect of treatment assignment on the secondary outcomes, such as BMI, waist circumference, serum lipid profile, fasting glucose, and glycosylated hemoglobin (HbA1c) will be evaluated using the linear mixed modeling approach described above. The proportion of subjects achieving 3, 4, or 5% weight loss will be compared between the treatment groups with the Fisher's Exact test. Type 1 error for secondary outcomes will be adjusted using the Bonferroni correction, basing the adjustment on the number of conceptually related statistical tests.

Other Outcomes: Schizophrenia symptoms (BPRS), depression (BDI), dietary consumption (TFEQ), exercise (YPAS), quality of life (Q-LES-Q and SF-36), cognition (MATRICS) and metabolism/inflammation markers will be obtained as presented in table 3. Summary statistics (frequencies, percents, means and standard deviations, and medians and interquartile ranges) will be calculated for naltrexone vs. placebo at each time point. Appropriate parametric (for normally distributed data) and non-parametric (deviation from normality in data distribution) approaches will be used to ascertain clinically meaningful group differences at each time point. Depending upon the distribution of these outcomes, the effect of naltrexone vs. placebo on change over time in each outcome will also be examined with GLMM, making appropriate model selections for either binary or continuous outcomes.
Using UKU Side Effect Checklist and C-SSRS we will list and summarize side effects and suicidal tendencies reported in each treatment group. Medication changes that could not be avoided during the study will be examined in three groups: no change, change from a higher weight liability to a lower weight liability medication, and vice versa. Weight liability rankings of antipsychotics will be based on Allison and Newcomer. Distributions of all variables will be evaluated for normality. Alternative statistical approaches such as transformations or non-parametric tests will be used, as required.

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

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Naltrexone is an FDA approved medication with the indication of alcohol dependence.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA? N/A
b. Who holds the IND?
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☒ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☒ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☒ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☒ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☒ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
☐ Blood grouping serum

☐ Reagent red blood cells
☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Pharmacodynamic Actions: Naltrexone is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids. When co-administered with morphine, on a chronic basis, naltrexone blocks the physical dependence to morphine, heroin and other opioids. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of naltrexone is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, naltrexone will precipitate withdrawal symptomatology. Clinical studies indicate that 50 mg of naltrexone hydrochloride will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of naltrexone hydrochloride provides blockade for 48 hours, and tripling the dose of naltrexone hydrochloride provides blockade for about 72 hours.

Naltrexone blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

The mechanism of action of naltrexone in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and naltrexone has been shown to reduce alcohol consumption in clinical studies.

Naltrexone is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Clinical Trials: Alcoholism: The efficacy of naltrexone as an aid to the treatment of alcoholism was tested in placebo-controlled, outpatient, double blind trials. These studies used a dose of naltrexone hydrochloride 50 mg once daily for 12 weeks as an adjunct to social and psychotherapeutic methods when given under conditions that enhanced patient compliance. Patients with psychosis, dementia, and secondary psychiatric diagnoses were excluded from these studies.

In one of these studies, 104 alcohol-dependent patients were randomized to receive either naltrexone hydrochloride 50 mg once daily or placebo. In this study, naltrexone proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving naltrexone were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of naltrexone as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter safety study. This study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications, polysubstance abuse and HIV disease. Results of this study demonstrated that the side effect profile of naltrexone appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon.

In the clinical studies, treatment with naltrexone supported abstinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abstinence and relapse were similar to those observed in the controlled studies. Naltrexone was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

Treatment of Opioid Addiction: Naltrexone has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

There are no data that demonstrate an unequivocally beneficial effect of naltrexone on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.

The drug is reported to be of greatest use in good prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative program, behavioral contract, or other compliance-enhancing protocol. Naltrexone, unlike methadone or LAAM (levo-alpha-acetyl-methadol), does not reinforce medication compliance and is expected to have a therapeutic effect only when given under external conditions that support continued use of the medication.

Dosage: Treatment of Alcoholism: The placebo-controlled studies that demonstrated the efficacy of naltrexone as an adjunctive treatment of alcoholism used a dose regimen of naltrexone hydrochloride

50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not studied in these trials.

Physicians are advised that 5% to 15% of patients taking naltrexone for alcoholism will complain of non-specific side effects, chiefly gastrointestinal upset. Prescribing physicians have tried using an initial 25 mg dose, splitting the daily dose, and adjusting the time of dosing with limited success. No dose or pattern of dosing has been shown to be more effective than any other in reducing these complaints for all patients.

Treatment of Opioid Dependence: Once the patient has been started on naltrexone hydrochloride, 50 mg once a day will produce adequate clinical blockade of the actions of parenterally administered opioids. As with many non-agonist treatments for addiction, naltrexone is of proven value only when given as part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

A flexible approach to a dosing regimen may be employed to enhance compliance. Thus, patients may receive 50 mg of naltrexone hydrochloride every weekday with a 100 mg dose on Saturday or patients may receive 100 mg every other day, or 150 mg every third day. Several of the clinical studies reported in the literature have employed the following dosing regimen: 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday. This dosing schedule appeared to be acceptable to many naltrexone patients successfully maintaining their opioid-free state.

Experience with the supervised administration of a number of potentially hepatotoxic agents suggests that supervised administration and single doses of naltrexone hydrochloride higher than 50 mg may have an associated increased risk of hepatocellular injury, even though three-times a week dosing has been well tolerated in the addict population and in initial clinical trials in alcoholism. Clinics using this approach should balance the possible risks against the probable benefits and may wish to maintain a higher index of suspicion for drug-associated hepatitis and ensure patients are advised of the need to report non-specific abdominal complaints.

CONTRAINDICATIONS

Naltrexone is contraindicated in:

1. Patients receiving opioid analgesics.
2. Patients currently dependent on opioids, including those currently maintained on opiate agonists [e.g., methadone or LAAM (levo-alpha-acetyl-methadol)].
3. Patients in acute opioid withdrawal
4. Any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids.
5. Any individual with a history of sensitivity to naltrexone or any other components of this product.
6. Any individual with acute hepatitis or liver failure.

WARNINGS

Hepatotoxicity:

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses.

Patients will be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.

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

   CMHC Research Pharmacy

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

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.

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. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
      No other medications are approved or proven to be efficacious for antipsychotic weight gain.
   b. State the maximum total length of time a participant may receive placebo while on the study.
      52 weeks
   c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.
      Placebo, in this case, is equal to treatment as usual.
   d. Describe the procedures that are in place to safeguard participants receiving placebo.
      Weekly (for the first 4 weeks) and every other week for the remainder – MD check ins/safety visits

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *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 If no, explain why this is acceptable. Patients may not continue taking the study medication after their participation in the study has ended, however, if they are free to discuss taking naltrexone in an un-blinded manner with their primary physician, who should make the decision as to whether this is appropriate to do.

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol 200

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	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐ YCCI Recruitment database	☐ Clinicaltrials.gov Registry (do not send materials to HIC)	
☒ Other (describe): Clinician Referrals		

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Potential subjects will either self-identify by seeing a flyer and contacting us with their interest, or their clinician may identify them as potentially eligible and give them our contact information. Familiar patients who have done multiple studies with us or who are patients of Dr. Tek may be identified by research staff as potentially eligible.

b. Describe how potential subjects are contacted.

Potential subjects will contact research staff in order to complete a telephone screening procedure that will determine eligibility. At that point, we will get permission from the patient to contact them further about the study, via telephone or through their clinician. If a potential subject has been in one of our studies in the past and has given permission to be contacted about future studies, research staff will call them to see if they are interested.

c. Who is recruiting potential subjects?

Cenk Tek, Vinod Srihari, Erin Reutenauer, Ismail Sinan Guloksuz, Suat Kucukgoncu, Katherine Lucas

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:

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

☐ 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.
Subjects are clinically stable outpatients with SMI who are followed up in the PI's clinic within CMHC.

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;
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;
It would be impractical to obtain a subject's authorization, as the initial PHI we collect from them is obtained over the phone. This information is kept in a locked, secure filing cabinet and is not shared with anyone outside of 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 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.

Tek, Srihari, Reutenauer, Guloksuz, Kucukgoncu, Lucas

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 procedures, risks and benefits of the study will be discussed in detail during a face to face interview with the subject. Subjects will be given the consent for to review. Consent staff will be available in person to answer all questions at that time.

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.

Subjects with limited decision making capacity will not be enrolled.

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.

Adult compound consent form for patient volunteers will be employed.

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.

Non-English speaking subjects will not be enrolled

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

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?

PHI that will be collected includes name, date of birth, and other demographic variables. Access to existing CMHC clinical charts will be authorized by release of information. This information will be used solely for access to diagnosis and medication information and not for research data collection purposes.

Some PHI will become part of a separate CMHC medical record. If a participant does not already have a medical record at CMHC, one will be created. The information that will be entered into the medical record will include the following: a copy of your signed informed consent and a Research Tracking for CMHC Patients Form which states information about the patient's participation in this study for chart records including the title of the research study, duration of their participation, and if the study involves taking a medication/placebo. No information regarding the results of drug testing will be included in the CMHC medical record.

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

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 data will be kept in locked confidential files in locked offices at the Connecticut Mental Health Center or on the secure Yale or CMHC server. Computerized data will be password protected and only researchers involved in the study will have access to it. For purposes of data analysis and publication, only identification numbers will identify subjects. In all records of this study, participants will be identified by a number, and their name will be known only to the researchers. The principal investigator will keep a link that identifies the participant and their coded information, but this link (key) will be kept secure and available only to the PI or selected members of the research team and will be kept in a different physical location than the coded data. At the end of the study, any personal identifying information will be destroyed.

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.

At the end of the study, any personal identifying information will be destroyed. We will utilize the expertise of the Yale ITS to perform approved degaussing procedures in order to fully destroy any electronic and physical data remaining at the end of the study.

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)

National Institutes of Health (NIH), Tek, Srihari, Reutenauer, Guloksuz, Kucukgoncu, Lucas

g. If appropriate, has a Certificate of Confidentiality been obtained?

An application was submitted to NIDDK for a certificate of confidentiality. The Coc was granted on April 8, 2013 and is set to expire February 28, 2018.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? No (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. N/A

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Obesity is an important health risk. Modest decreases of body weight (4% total body weight) in overweight individuals decrease risk for development of diabetes and cardiovascular disease as much as fifty percent. Prevention of development of these illnesses will increase subjects' quality of life, decrease morbidity and mortality as well as decrease health care expenditures for the overall society.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

Subjects can enroll in available weight loss and exercise programs at CMHC, community, and through their primary care providers.

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 in cash at each in person appointment. The baseline procedures will span 3 appointments, for which they will receive $15 each time ($45 total). Following enrollment, subjects will be seen weekly for the first 4 weeks. They will be paid $5 each for weeks 1-3. After the first 4 weeks, subjects will attend appointments every other week. They will be paid $10 for these appointments and

on an escalating payment for each monthly milestone ($15, $20, $25, $30, $35…$70). The total amount a subject can earn for completing the entire study is $700.

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.

   There is no cost to the subject.

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, medical care will be provided for physical injury or illness that occurs as a direct result of subject participation in this study.
   b. Where and from whom may treatment be obtained?
      The PI is responsible to make the necessary referrals to Yale University/YNHH clinics or patient's own primary care physician.
   c. Are there any limits to the treatment being provided?
      No
   d. Who will pay for this treatment?
      There are no funds available for compensation of care. The patient and/or their insurance will be responsible for treatment for any study related injury.
   e. How will the medical treatment be accessed by subjects?
      Referral by the PI.