HIC 1606017928

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: A Pilot Study of Naltrexone – Bupropion combination versus Placebo Combined with Bupropion for Weight Loss in Comorbid Schizophrenia			
Principal Investigator: Cenk Tek, MD		**Yale Academic Appointment:** Associate Professor	
Campus Address: 34 Park Street, 267B, New Haven, CT 06519			
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Protocol Correspondent Name & Address (*if different than PI*): Erin Sullivan 34 Park Street, Rm. 10 New Haven, CT 06519			
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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:

APPROVED BY THE YALE UNIVERSITY IRB 6/13/2018 VALID THROUGH 7/4/2019

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

o 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.

3 years (2016-2019)

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.

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.

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 combining open-label extended release bupropion (flexible dosing up to 450mg target) and naltrexone (37.5mg) versus Bupropion and placebo along with a daily 500 calorie reduction diet recommendation for weight and health risk reduction in 40 overweight/obese individuals with schizophrenia.

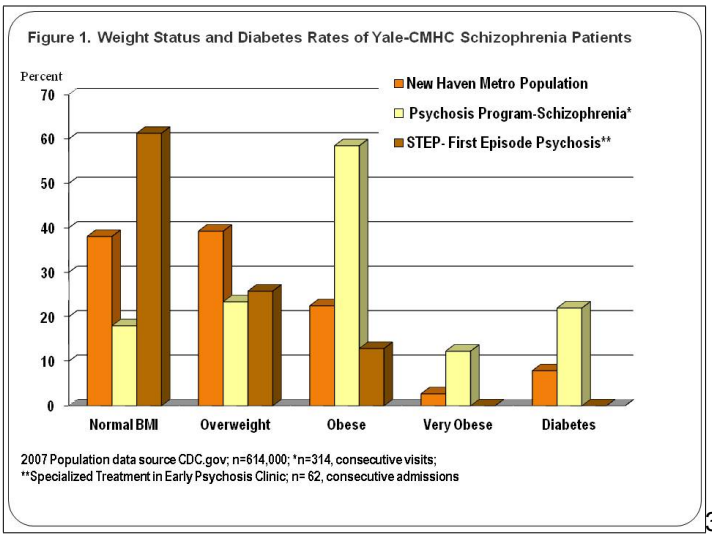
Hypothesis 1: Subjects receiving extended release bupropion (150mg-450mg) and naltrexone 37.5mg for 16 weeks will reduce weight, and improve body mass index (BMI) and waist circumference, at a greater level than the subjects who receive bupropion and placebo.

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

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 psychotic disorders die on average 25 years earlier than the general population[1-3]. Most of this premature mortality is attributed to cardiovascular disease (CVD) [4-6]. Additionally, overweight/obesity results in insulin resistance and subsequently Type II Diabetes Mellitus (DM). DM can in turn cause widespread inflammation and organ failure including increased cardiovascular risk through increased atherosclerosis and cardiac tissue and blood vessel damage. These direct results of overweight/obesity are sometimes called metabolic syndrome in aggregate. In sum, increased adiposity or overweight/obesity is the most important modifiable cause of increased cardiovascular morbidity and mortality, besides two other independent atherosclerosis increasing factors, namely genetic disposition (non-modifiable) and smoking (modifiable)[7-9]. Obesity is associated with a major burden of disease and is strongly associated with increased cardiovascular mortality[10]. As such, obesity is a leading cause of preventable death in the United States, second only to smoking, and the primary cause of preventable cardiovascular death[11].

Obesity and Diabetes rates in psychiatric populations are much higher than the general population[5,12,13]. 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 were about three times higher among patients with long standing schizophrenia than the general population. Obesity is associated with significantly increased outpatient medical costs (25%)[14,15]. Both



schizophrenia and obesity are associated with significant stigma, and discrimination at work or in society[16,17]. In a recent study, we showed that schizophrenia patients are impacted more from the stigma of obesity than the stigma of mental illness[18]. Obesity in schizophrenia has been associated with additional decline in quality of life[19] and improvement has been shown with weight loss[20,21].

Obesity in schizophrenia is closely associated with antipsychotic use[22-24]. Fig. 1, presented before, also depicts our initial first episode psychosis cohort, which did not have increased rates of obesity, or diabetes at the onset of their schizophrenia treatment. Indeed, in the first US effectiveness study of first episode psychosis treatment services (Specialized Treatment Early in Psychosis (STEP)), we have shown that the age adjusted cardiovascular risk for first episode patients is similar to population controls during initial assessment [25] . In a follow-up study, 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[26]. Our findings of very early increase in weight/adiposity and cardiovascular risk are now replicated in two large studies: the multi-national, multicenter European First Episode Schizophrenia trial (EUFEST) and US NIH funded multicenter Recovery After an Initial Schizophrenia Episode (RAISE)[27,28]. To confirm that early increase in weight and subsequent cardiovascular risk is indeed a treatment effect, we also conducted a meta-analysis of all pharmacological trials in first episode psychosis[29]. Compared to placebo, antipsychotics caused mean weight gain of 3.22 kg and 1.4 BMI points in the short-term (studies less than 6 months), and 5.30 kg and 1.86 BMI points in the long term (6 months to 1 year).

We have previously hypothesized that weight gain effect is possibly linked to dopamine 2 receptor blockade-related blunting of the human reward system via opiate receptors. D2 blockade is the only common characteristic of antipsychotic medications and the results of our meta-analysis, presented above, supported the D2 link. In a proof of concept trial, we have utilized a pure opioid antagonist, naltrexone at a dose estimated to block 70% of the opioid receptors in the brain. We have hypothesized that this would either upregulate and increase the sensitivity of opioid receptors and cause optimal food reward to be reached with less eating, or alternatively would make it difficult to reach the optimal food reward; thus subjects would stop overeating to reach the threshold. The strategy worked for non-diabetic antipsychotic users who were gaining weight and resulted in 4.8kg weight loss on average compared to 1.38kg weight gain in placebo arm. Diabetic patients who were similar in disease characteristics, antipsychotic dose, extent of weight gain, and demographics to non-diabetic subjects did not lose weight[30]. Based on this premise, we are conducting a large NIH funded clinical trial with non-diabetic antipsychotic users, which will both answer the question of efficacy of naltrexone for antipsychotic-induced weight gain, but also the utility of blocking all vs. groups of opioid receptors to counteract D2 blocker-induced weight gain[31].

During this timeframe, a combination of naltrexone with noradrenaline/dopamine reuptake blocker bupropion has been developed and FDA-approved for the treatment of obesity in the general population. Naltrexone does not normally produce weight loss in humans and bupropion produces modest weight loss, however the combination produces clinically significant weight loss, which appears to be more than the sum of its components would

otherwise produce separately [32-34]. Of interest to us, the combination has been shown to be effective for clinically significant weight loss in obese subjects with type 2 diabetes as well[35]. Registration studies by the manufacturer of the combination pill excluded antipsychotic medication users, thus we have no information on the potential effectiveness of the combination in this population. Both naltrexone and bupropion are commonly used in psychiatry, naltrexone for co-morbid alcohol addiction, and bupropion for co-morbid depression and/or cigarette addiction. The PI and the research coordinator (Dr. Tek and Ms. Sullivan) were also members of the Yale team that conducted a large clinical trial of bupropion for smoking cessation in schizophrenia[36]. Thus we have extensive experience in the use of both medications in schizophrenia. Here we are proposing a 16-week pilot trial of 37.5mg naltrexone/placebo added to extended release bupropion in flexible dosing (150mg to 450mg) and a daily 500 calorie reduction diet recommendation for subjects with schizophrenia and obesity. A dose of 37.5mg is similar to the FDA-approved combination dose for naltrexone. However, based on our experience with bupropion, we have chosen to use bupropion in an un-blinded manner and reach the target dose of 450mg based on tolerance of the individual subject over the initial 3-week period.

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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.

All subjects will be prescribed open-label bupropion extended release (XR, 150mg initial dose, increased as tolerated up to 450mg target dose over the initial 3 weeks of the study). Additionally, subjects will be randomized to active Naltrexone 37.5mg or placebo groups in a 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 diabetes status to ensure equal numbers in each arm across diagnosis.

Following study screening and baseline procedures, subjects will take the study medications daily for 16 weeks. At baseline a review of patient's daily diet will be conducted by a 24 hour food recall. Inquiries will also be made on past week's consumption of calorie-dense snack food and sugar-containing drinks. Based on a review, subjects will be instructed on how they can cut their daily calorie consumption by 500 calories. 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 12 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 are taking bupropion and 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).

All potential subjects will meet with study staff for intake and evaluation sessions to determine eligibility prior to enrollment. Following consent procedures, subjects' clinicians will be contacted by telephone to inform them about study participation as well as to inquire about the inclusion criteria. This has been the standard operating procedure for clinical trials conducted by this team. All participants will be carefully assessed for mood symptoms by the study psychiatrist at baseline and throughout the study duration.

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 opioid use. 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. 9) Resting Metabolic Rate (**RMR**) is calculated through a mathematical formula not indirect calorimetry. No special procedure is utilized that would be bothersome to subjects. 10) 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. 11) 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. 12) Fagerstrom Test of Nicotine Dependence **(FTND)** is a standard instrument for assessing the intensity of physical addiction to nicotine. It contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence. 13) 24-Hour Diet Recall **(Food Recall)** is a quantitative research method (interview) used in nutritional assessment, which asks individuals to recall

foods and beverages they consumed in the twenty-four hours prior to the interview. 14) The Brief Negative Symptom Scale **(BNSS)** is a 13-item instrument designed for clinical trials and other studies designed to measure blunted affect, alogia, asociality, anhedonia, and avolition. 15) Cognitive Tests (a) Letter-Number Sequencing Task **(LNS)** is a brief, standardized executive function task used to assess verbal working memory performance. The test involves a 24-item Experimental Condition, in which participants are read a series of letters and numbers and asked to recite both back in ascending order, with the numbers first and then the letters. and (b) Digit Symbol Substitution Test **(DSST)** is a common neuropsychological test that requires the examinee to transcribe a unique geometric symbol with its corresponding Arabic number. The examinee is initially shown a key containing the numbers from 1 to 9. Under each number there is a corresponding geometric symbol. The examinee is then shown a series of boxes containing numbers in the top boxes, and blank boxes below them. After a short practice trial, they are then asked to copy the corresponding geometric symbol under each number.

Assessment Schedule:

	Screen	Baseline	Weeks 1-3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
Consent/CMHC docs	X									
SCID, Demo	X									
Urine Tox, HCG Preg	X	X		X		X		X		X
Vitals, Weight, WC	X	X	X	X	X	X	X	X	X	X
Blood tests	X									X
RMR		X		X		X		X		X
24 Hour Food Recall & 500 calorie reduction discussion		X				X				X
TFEQ, FTND	X			X		X		X		X
BPRS	X			X		X		X		X
BDI, C-SSRS	X			X		X		X		X
BNSS	X					X				X
UKU, med check	X	X	X	X	X	X	X	X	X	X
LNS, DSST		X								X
Start Study Meds		X								

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

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.

40 overweight/obese patients with schizophrenia.

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 16 weeks 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.	The study doctor and research team will know which medication I'm taking during the study.	T____ F _X_

7. Please circle the names of the study medication that you may receive in this study.

Haldol	Bupropion	Mellaril
Naltrexone	Paxil	Placebo

8. I can stop being in the study any time that I want. T_X_ F ____
9. 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 ____
10. One of the possible side effects of the study medication(s) is nausea 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 or schizoaffective disorder based on SCID interview (If bipolar-schizoaffective: need to be adequately stabilized on a mood stabilizer and show no mania history for the past one year, as confirmed by study psychiatrist and patient's clinician)
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.) Note: All subjects will be screened for drugs, not only those suspected of opiate use.
2) A history of seizures in the past five years (confirmed through chart review and discussion with patient's clinician)
3) Meet DSM criteria for Bipolar Disorder
4) History of mania in the past one year (confirmed through chart review and discussion with patient's clinician)
5) Uncontrolled hypertension
6) Current history of dementia, mental retardation
7) Not capable of giving informed consent for participation in the study
8) Women who are pregnant or breast-feeding
9) Physical conditions affecting body weight (e.g. Cushing's disease, polycystic ovary syndrome)
10) Severe liver dysfunction, (serum aminotransferases greater than three times normal), acute infectious hepatitis, liver failure.
11) History of glaucoma.

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.

Bupropion and Bupropion/Naltrexone combination:

Small increased risk of depression, suicidal ideation, and suicide: Due to the small increased incidence of depression, suicidal ideation, attempts, and completed suicides in people having taken Naltrexone and Bupropion separately (but not in combination studies), we will monitor this risk using the Columbia Suicide Severity Rating Scale as well as regular check-ins /mood evaluations with the study psychiatrist through study participation. If, during screening or throughout the trial, a patient indicates 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.

Risk of seizure: Bupropion can cause seizures. The risk is decreased by extended-release formulations. The extended-release formulation of bupropion that will be used in this study has a seizure incidence of 0.1%. The risk of seizure is dose-related. The incidence of seizure in patients receiving the Bupropion Naltrexone combination in clinical trials was approximately 0.1% vs 0% on placebo. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. We will exclude patients with any history of seizures.

Increase in Blood Pressure and Heart Rate: Bupropion alone or bupropion naltrexone combination can cause an increase in systolic and/or diastolic blood pressure as well as an increase in resting heart rate. In clinical practice with other bupropion-containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. Blood pressure and heart rate in all patients, will be closely monitored throughout the trial.

Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction has been observed with naltrexone alone at doses 10 to12 times the study dose. No hepatotoxicity has been reported at or twice the study dose nor with the combination pill.

Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. The Bupropion alone or Bupropion Naltrexone combination can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Subjects with glaucoma will be excluded from the study.

Use of Antidiabetic Medications: Weight loss may cause hypoglycemia. As some study participants will be patients with type 2 diabetes mellitus on antidiabetic therapy, they will be advised to monitor their blood glucose levels and report symptoms of hypoglycemia to the study doctor as well as their healthcare provider(s) throughout the study. Blood glucose levels, insulin levels and hemoglobin A1c levels will be obtained prior to start the study medication and again at study endpoint.

Opioid Withdrawal: Naltrexone alone or in the combination 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. Opiate using subjects will be excluded from the study. Subjects will be warned about the interaction.

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.

Other Side Effects: The most common other side effects of the bupropion naltrexone combination or each medication alone are nausea, dizziness, constipation, trouble sleeping, headache, dry mouth, vomiting, and diarrhea.
Exposure during Pregnancy: Both bupropion and naltrexone are pregnancy Category C medications 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. Bupropion is associated with heart defects in one study, but this was not confirmed in the manufacturer's pregnancy database and subsequent studies. The Bupropion Naltrexone combination is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. 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 this population. 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.

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 and bupropion dosages we use are at and below the FDA approved dose and these drugs have 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. The principal investigator is responsible for monitoring the data, assuring protocol compliance. Dr Susan Parke, an experienced psychiatrist, will act as a safety officer and will be conducting safety reviews with the investigators twice a year. 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). 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.

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), 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), and the FDA (as appropriate) within 5 calendar days of it becoming known to the investigator, using the appropriate forms found on the website.

The safety officer (Susan Parke 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.

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 double-entered into SPSS 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. Neither Mr. Pittman, nor Dr. Gueorguieva will have access to subject identifiers. 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.

Hypothesis Testing: The primary goal of this study is to compare the weight changes resulting from naltrexone compared to placebo in combination with bupropion. The primary ITT analysis 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).

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).

Bupropion is an FDA approved medicine with the indication of depression (Wellbutrin) and smoking cessation (Zyban).
Naltrexone is an FDA approved medication with the indication of alcohol dependence. Intramuscular depot formulation of naltrexone is also approved for treatment of opiate dependence.
Naltrexone-bupropion combination is approved by the FDA for treatment of obesity.

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.

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.

Bupropion HCl is an aminoketone class antidepressant. It inhibits weakly the neuronal uptake of dopamine and norepinephrine, but does not inhibit monoamine oxidase or the reuptake of serotonin. Although the exact mechanism of action in smoking cessation is unclear, it is thought to be mediated by the noradrenergic and/or dopaminergic effects of bupropion.

The combination of these two medications is thought to act to regulate food intake by increasing the firing rate of the hypothalamic pro-opiomelanocortin neurons (appetite regulatory center) and the mesolimbic dopamine circuit (rewards system). The exact mechanism is not fully understood.

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

Clinical Trials:

The Naltrexone Bupropion combination was evaluated for safety in five double-blind placebo controlled trials in 4,754 overweight or obese patients (3,239 patients treated with THE NALTREXONE BUPROPION COMBINATION and 1,515 patients treated with placebo) for a treatment period up to 56 weeks. The majority of patients were treated with The Naltrexone Bupropion combination 32 mg/360 mg total daily dose. In addition, some patients were treated with other combination daily doses including naltrexone up to 50 mg and bupropion up to 400 mg. All subjects received study drug in addition to diet and exercise counseling. One trial (N=793) evaluated patients participating in an intensive behavioral modification program and another trial (N= 505) evaluated patients with type 2 diabetes. In these randomized, placebo-controlled trials, 2,545 patients received The Naltrexone Bupropion combination 32 mg/360 mg for a mean treatment duration of 36 weeks (median, 56 weeks). Baseline patient characteristics included a mean age of 46 years, 82% women, 78% white, 25% with hypertension, 13% with type 2 diabetes, 56% with dyslipidemia, 25% with BMI greater than 40 kg/m2, and less than 2% with coronary artery disease. Dosing was initiated and increased weekly to reach the maintenance dose within 4 weeks. In The Naltrexone Bupropion combination clinical trials, 24% of subjects receiving The Naltrexone Bupropion combination and 12% of subjects receiving placebo discontinued treatment because of an adverse event. The most frequent adverse reactions leading to discontinuation The Naltrexone Bupropion combination were nausea (6.3%), headache (1.7%) and vomiting (1.1%).

The most commonly reported side effects associated with taking The Naltrexone Bupropion combination in completed clinical trials of overweight and obese individuals were: Nausea (32.5%), Constipation (19.2%), Headache (17.6%), Vomiting (10.7%), Dizziness (9.9%), Insomnia (9.2%), Dry Mouth (8.1%), Diarrhea (7.1%), Anxiety (4.2%), Hot flush (4.2%), Fatigue (4.0%), Tremor (4.0%).

In placebo-controlled clinical trials with the Naltrexone Bupropion combination for the treatment of obesity in adult patients, no suicides or suicide attempts were reported in studies up to 56 weeks in duration (equivalent to bupropion doses of 360 mg/day). In these same studies, suicidal ideation was reported by 3 (0.20%) of 1,515 patients treated with placebo compared with 1 (0.03%) of 3,239 treated with the Naltrexone Bupropion combination.

The incidence of seizure in patients receiving the Naltrexone Bupropion combination in clinical trials was approximately 0.1% vs 0% on placebo. The Naltrexone Bupropion combination should be discontinued and not restarted in patients who experience a seizure while being treated with Naltrexone and/or Bupropion.

The Naltrexone Bupropion combination can cause an increase in systolic and/or diastolic blood pressure as well as an increase in resting heart rate. Among patients treated with this combination medication in placebo-controlled clinical trials, mean systolic and diastolic blood pressure was approximately 1 mmHg higher than baseline at Weeks 4 and 8, similar to baseline at Week 12, and approximately 1 mmHg below baseline between Weeks 24 and 56. In contrast, among patients treated with placebo, mean blood pressure was approximately 2 to 3 mmHg below baseline throughout the same time points, yielding statistically significant differences between the groups at every assessment during this period. The largest mean differences between the groups were observed during the first 12 weeks (treatment difference +1.8 to +2.4 mmHg systolic, all $p<0.001$; +1.7 to +2.1 mmHg diastolic, all $p<0.001$). For heart rate, at both Weeks 4 and 8, mean heart rate was statistically significantly higher (2.1 bpm) in the Naltrexone Bupropion combination group compared with the placebo group; at Week 52, the difference between groups was +1.7 bpm ($p<0.001$).

In the one-year controlled trials of the Naltrexone Bupropion combination, the proportion of patients reporting one or more adverse reactions related to psychiatric and sleep disorders was higher in the Combination (32/360 mg) group than the placebo group (22.2% and 15.5%, respectively). These events were further categorized into sleep disorders (13.8% Combination, 8.4% placebo), depression (6.3% Combination, 5.9% placebo), and anxiety (6.1% Combination, 4.4% placebo). Patients who were 65 years or older experienced more psychiatric and sleep disorder adverse reactions in the Combination group (28.6%) compared to placebo (6.3%), although the sample size in this subgroup was small (56 Combination, 32 placebo); the majority of these events were insomnia (10.7% Combination, 3.1% placebo) and depression (7.1% Combination, 3.1% placebo).

Dosing: The Naltrexone Bupropion combination should be escalated slowly, typically over a 3 to 4 week period until full dosing is reached. The Naltrexone Bupropion combination should be taken by mouth in the morning and in the evening. The tablets should not be cut, chewed, or crushed. In clinical trials, the combination was administered with meals. However, The Naltrexone Bupropion combination should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure.

CONTRAINDICATIONS

The Naltrexone Bupropion combination is contraindicated in:

- Uncontrolled hypertension
- Seizure disorder or a history of seizures
- Use of other bupropion-containing products (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, ZYBAN, and APLENZIN)
- Bulimia or anorexia nervosa, which increase the risk for seizure
- Chronic opioid or opiate agonist (e.g., methadone) or partial agonists (e.g., buprenorphine) use, or acute opiate withdrawal
- Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs

- Concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with this medication combination. There is an increased risk of hypertensive reactions when the Naltrexone Bupropion combination is used concomitantly with MAOIs. Use in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated
- Known allergy to bupropion and/or naltrexone
- Anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion
- Pregnancy

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.
      16 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 monthly 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, they are free to discuss taking naltrexone and/or bupropion 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_40__

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 initial 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?
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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:

Health information that will be collected over the telephone includes self-reported psychiatric diagnosis, self-reported height and weight, and self-reported medication list. All other medical information will be requested after informed consent.

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 schizophrenia or schizoaffective disorder 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. In the initial phone interview, we will collect name, age, diabetes and schizophrenia status. Self reported height and weight, as well as a list of medications will be inquired to confirm eligibility.

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.

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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 form 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. This will be determined by performance on the consent quiz as well as through discussion with their clinician and study psychiatrist.

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 after five years, however anonymous data will be kept indefinitely.

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 after five years. 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)

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

An application for a certificate of confidentiality has been submitted to National Institute of Mental Health (NIMH) and was approved on April 5, 2017.

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 cardiovascular disease risk by 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. In order to determine study eligibility participants will come in for a screening appointment for which they will be paid $5, if they appear eligible at that point they will be invited to a baseline assessment for which they will receive $10. 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 once every two weeks. They will be paid for each monthly appointment on an escalating scale (week 4 $10, week 8 $15, week 12 $20, week 16 $25). In between each month visit, there will be quick check-in appointments for which subjects will be paid $5 each (weeks 6, 10 &14). The total amount a subject can earn for completing the entire study is $115.

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.