NCT03045341

Behavioral and Pharmacologic Treatment of Binge Eating and Obesity

Document date: 10/28/2020

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: 1506016065 - Behavioral and Pharmacologic Treatment of Binge Eating and Obesity			
Principal Investigator: Carlos M. Grilo, Ph.D.		**Yale Academic Appointment:** Professor of Psychiatry and Psychology Director of Yale Program for Obesity, Weight, and Eating Research	
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Faculty Advisor:*(required if PI is a student, resident, fellow or other trainee)* ☒ **N/A**		**Yale Academic Appointment:**	
Campus Address:			
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Date: 10/7/2020, Version 11

Investigator Interests:

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

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degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
☐ Yes☒ **No**

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
☐ Yes☒ **No**

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

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

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

SECTION II: GENERAL INFORMATION

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

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus
☒ **Other Yale Location: Yale Program for Obesity, Weight, and Eating Research, 301 Cedar St, 2nd Floor; Yale Department of Psychiatry**

b. External Location[s]:

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☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☒ **Other Location: Quest Diagnostics** Lawrence-Memorial Hospital
☐ 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:
☐ Yale University RSC (YU-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ *Nursing Research Committee Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

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

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
September 2016 – September 2023

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:

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

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

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

If yes, where is it registered?
Clinical Trials.gov registry ☒
Other (*Specify*)

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

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

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

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

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding*

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mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

Yes ☐ **No**☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?

   Yes ☐ **No**☒

   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 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

   Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. *Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and*

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Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Carlos M. Grilo	Behavioral and Pharmacologic Treatment of Binge Eating and Obesity	NIH/ NIDDK	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☒Grant-M# 2 R01 DK49587-16 ☐Contract# ☐Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***
☒ **N/A**

Send IRB Review Fee Invoice To:
Name:
Company:
Address:

Research Team: Please see IRES.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR 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.

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- 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.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

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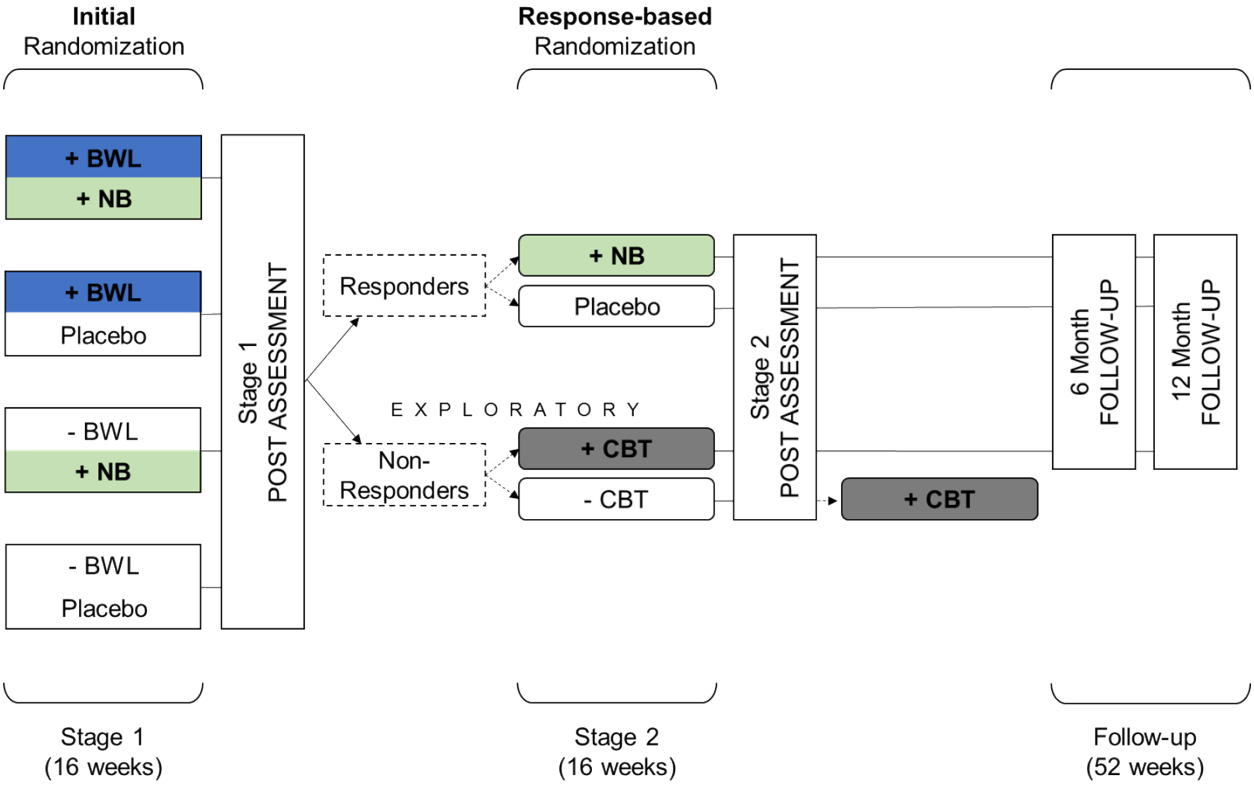
SECTION V: RESEARCH PLAN

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

This study aims to perform a two-stage randomized controlled trial to test the effectiveness of behavioral weight loss (**BWL**) and pharmacotherapy (Naltrexone/Bupropion; **NB**), alone and in combination, for the treatment of binge eating disorder (BED) in patients with obesity.

Figure 1. Research design of two-stage trial of BWL and NB for BED in patients with obesity



The **first stage** will examine the effectiveness of NB medication with and without BWL in reducing both binge eating and weight (See Figure 1).

(1) **Stage 1 RCT – Primary Aim -** Test effectiveness of BWL and NB medication, alone and combined, for BED. Primary aims are to evaluate the effectiveness for **(a)** reducing binge eating and **(b)** reducing weight.
(2) **Stage 1 RCT – Secondary Aims: (a)** Examine effectiveness of BWL and NB medication, alone and combined, on secondary outcomes: remission (zero binges/ 28 days), eating-disorder pathology, depression; and **(b)** Explore predictors, moderators, and mediators of primary outcomes.

The **second stage** will examine whether continued NB medication results in superior maintenance and longer-term outcomes than placebo *amongst responders to Stage 1 treatments*. The second stage will also explore whether adding cognitive-behavioral therapy (**CBT**) enhances on-going pharmacotherapy (NB/placebo), *amongst non-responders to Stage 1 treatments* (See Figure 1).

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(3) **Stage 2 RCT – Secondary Aims:** Examine the effectiveness of NB medication amongst responders to Stage 1 treatments for enhancing maintenance and longer-term **(a)** change in binge eating frequency and **(b)** weight change.
(4) **Stage 2 RCT – Exploratory Aims: (a)** Explore the effectiveness of NB medication on secondary outcomes: relapse to BED threshold, eating pathology, depression, psychosocial and metabolic functioning; and **(b)** Explore whether Stage 1 treatment moderates medication effects during Stage 2.
(5) **Stage 2 RCT – Exploratory Aim: CBT for Non-Responders:** Explore, *amongst Non-responders* to Stage 1 treatments, whether adding CBT enhances on-going NB pharmacotherapy.

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

Obesity (OB) is a refractory, serious public health problem, and an estimated 34% of U.S. adults have obesity (Flegal, Carroll, Ogden, & Curtin, 2010). This study proposes to test treatments for a high-risk subgroup of adults with OB, adults with binge-eating disorder (BED) and OB (Hudson, Hiripi, Pope, & Kessler, 2007).

Binge-Eating Disorder (BED) – A Clinical Subgroup of People with Obesity

BED is a formal diagnosis in the *DSM-5* (American Psychiatric Association, 2013). BED is defined by recurrent episodes of binge eating (eating an unusually large amount of while experiencing a subjective sense of loss of control) without compensatory weight control methods (e.g., self-induced vomiting) that characterize bulimia nervosa. The BED diagnosis requires binge eating to be associated with marked distress. Epidemiologic studies have found that BED is more prevalent than anorexia and bulimia nervosa (Hudson et al., 2007; Kessler et al., 2013). The prevalence of BED in the National Co-morbidity Survey Replication (Hudson et al., 2007) was 3.5% among women and 2.0% among men. Estimates of BED are higher in adults with obesity (8%) and much higher in most clinical settings (Johnson, Spitzer, & Williams, 2001; Wilfley, Wilson, & Agras, 2003). Compared to other eating disorders, BED is prevalent across gender and ethnic/racial groups (Marques et al., 2011). BED has diagnostic validity (Striegel-Moore & Franko, 2008), is a stable construct (Pope et al., 2006), differs from other eating disorders and obesity (Allison, Grilo, Masheb, & Stunkard, 2005; Grilo et al., 2009; Grilo, Masheb, & White, 2010) and is ***strongly associated with obesity*** (Kessler et al., 2013) and elevated risk for medical, psychiatric, and psychosocial problems (Grilo et al., 2009; Grilo et al., 2010; Hudson et al., 2007; Hudson et al., 2010).

Treatment for BED: Current Status and Future Needs

Overall, several medications have short-term efficacy relative to placebo (Reas & Grilo, 2008) and certain psychological treatments have efficacy (Wilson, Grilo, & Vitousek, 2007) with important advantages over medication (alone or in combination) (Reas & Grilo, 2008).

Cognitive Behavioral Therapy (CBT) is the best-established treatment for BED (National Institutes of Clinical Excellence, 2004; Wilson et al., 2007). RCTs testing CBT

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report roughly 50% remission rates from binge eating (Grilo, Masheb, & Wilson, 2005; Grilo, Masheb, Wilson, Gueorguieva, & White, 2011). Improvements in binge eating are significantly superior to fluoxetine (Grilo, Masheb, & Wilson, 2005) and fluvoxamine (Ricca et al., 2001) and are durable for 12-months after CBT (Grilo, Crosby, Wilson, & Masheb, 2012). RCTs have provided further support for "specific" efficacy of CBT for BED, although CBT fails to produce weight loss (Grilo et al., 2011). The association between BED and obesity (Hudson et al., 2007) and possible heightened risk for developing future metabolic problems (Hudson et al., 2010) highlight the need to find methods to reduce weight–and binge eating–in this subgroup of people with obesity.

Behavioral Weight Loss (BWL) for BED may be more effective than CBT for producing weight loss while achieving comparable reductions in binge eating that are maintained through 12-month follow-ups (Grilo et al., 2011). Although longer-term follow-up suggests that improvements in binge eating and weight losses are less durable in BWL (Wilson, Wilfley, Agras, & Bryson, 2010), BWL is more widely available and has greater dissemination than "specialist" CBT methods, which are very limited in availability (Hart, Granillo, Jorm, & Paxton, 2011; Kazdin & Blase, 2011; Shafran et al., 2009; Wilson & Zandberg, 2012). BWL has the advantage of being available in many health service settings and delivered by diverse allied health-care workers (i.e., not just "specialists" and doctoral-level clinicians with CBT training). This is especially relevant for BED because few individuals with BED receive mental health services (Marques et al., 2011) and especially fewer receive specialist treatment (Wilson & Zandberg, 2012).

Pharmacotherapy for BED has received research attention, albeit nearly all RCTs have been of short duration and without follow-up period to establish durability (Reas & Grilo, 2008, 2014, 2015). Critical review and meta-analysis show that several drugs – working through varied mechanisms – have short-term efficacy relative to placebo for reducing binge eating and produce weight loss ranging from modest to none (Reas & Grilo, 2008). Placebo-controlled trials of anticonvulsants topiramate and zonisamide (Claudino et al., 2007; McElroy et al., 2003; McElroy et al., 2006) have reported effects for reducing both binge-eating and weight (average weight loss of roughly 3-4 kg compared to placebo), but have also shown high dropout and frequent adverse events that become near-universal and troubling with longer use (McElroy, Kotwal, Hudson, Nelson, & Keck, 2004). SSRI antidepressants, initially regarded as a potential treatment strategy (e.g., National Institutes of Clinical Excellence, 2004) are characterized by small effect sizes relative to placebo (Reas & Grilo, 2008), produce no weight loss at all (Grilo, Masheb, & Wilson, 2005) and are inferior to CBT (Grilo, Masheb, & Wilson, 2005; Ricca et al., 2001).

Lisdexamfetamine dimesylate (LDX) for BED. An important development was the FDA approval in January 2015 of a CNS stimulant, LDX, for the treatment of moderate-to-severe BED. Approval was based on findings from an integrated series of studies funded by the manufacturer. The phase II RCT demonstrated that 50mg and 70mg were superior to placebo (McElroy et al., 2016; McElroy et al., 2015) for reducing binge-eating days and reported binge-eating abstinence rates of LDX versus placebo (Study 1: 40% versus 14%; Study 2: 36% versus 13%) at the end of the 11-week treatments. Importantly, no longer-term follow-up are presently available.

We are not using LDX for several reasons. The binge remission outcomes for LDX at 11-weeks (McElroy et al., 2016) are less robust than those reliably produced by BWL

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for BED, and BWL outcomes are durable through 12-months post-treatment (Grilo, Masheb, & Crosby, 2012). Most importantly, although LDX was associated with weight loss (mean 4.9 kg) (McElroy et al., 2015), weight loss was examined as a safety measure, not a clinical outcome. The FDA approval and manufacturer product labeling included a Limitation of Use highlighting that *LDX is not indicated or recommended for weight loss.* This is because other CNS-stimulant sympathomimetic medications for weight loss have been associated with severe cardiovascular problems and the safety and efficacy of LDX for obesity have not been demonstrated.

Pharmacotherapy for Obesity. Sibutramine, which was effective for reducing *both* binge eating and weight in BED (Appolinario et al., 2003; Wilfley et al., 2008), was withdrawn from the market in 2010 due to cardiovascular concerns. This left orlistat as the sole FDA-approved anti-obesity medication for longer-term use (Vetter, Faulconbridge, Webb, & Wadden, 2010), until 2012. Placebo-controlled trials of orlistat for BED (Golay et al., 2005; Grilo, Masheb, & Salant, 2005) reported significant yet very modest effects for weight loss, but *not* for reducing binge eating when added to BWL or CBT. A recent RCT testing orlistat combined with BWL reported a moderator effect of significantly greater weight loss for orlistat than placebo for obesity without BED, but not for obesity with BED (Grilo & White, 2013).

The 2012 FDA approval of two new anti-obesity medications (phentermine/ topiramate and lorcaserin) (Colman et al., 2012; Miller, 2013) came after heated debate given significant concerns about limited efficacy and safety profiles, and questions about serious medical complications with longer use (Colman et al., 2012; Miller, 2013). The low rates of achieving 5% weight loss (less than 30% in all three of the phase III RCTs) was inflated due to the use of completer analyses despite the observed high drop-out rates (e.g., 45% in the BLOOM Trial) (Smith et al., 2010). The combination phentermine/topiramate had the highest effect sizes for weight loss, but this needs to be considered against the unfavorable adverse event and tolerability profile.

NB Pharmacotherapy

In September 2014, the FDA approved the combination of naltrexone and bupropion to treat obesity consisting of the following empirical support from several RCTs performed with obesity (but not BED). The putative mechanisms of action are described in Section VI (page 30).

Obesity Outcomes. Several large RCTs have reported that NB was effective in promoting significant, clinically-meaningful weight loss in patients with obesity (Greenway et al., 2010; Greenway, Whitehouse, et al., 2009; Smith et al., 2013). NB showed greater weight loss than placebo, -6.5 vs -1.2% (Greenway et al., 2010); -8.2% vs -2.1% (Smith et al., 2013), and the following percentages achieving 5% weight loss: 56% vs. 18% (Smith et al., 2013), 52% vs. 15% (Greenway et al., 2010). Apovian et al. (2013), in a study of 1496 patients with obesity, reported greater weight losses relative to placebo (-6.5% vs -1.9% at week 28 and -6.4% vs -1.2% at week 56) and greater likelihood of achieving 5% weight loss (56% vs 18% at 28 weeks).

C. **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**

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include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Figure 2. Participant Assessment and Classification Time Course.

Pre-Randomization	Stage 1	Stage 2	Follow-Up
• Response to Recruitment • Pre-Screening • Baseline Assessment	• Initial Randomization • Participation in Stage 1 • Stage 1 Post Assessment • Classification as Responder or Non-Responder	• Response-based Randomization • Participation in Stage 2 • Stage 2 Post Assessment	• 6-Month Follow-up Assessment • 12-Month Follow-Up Assessment

Pre-Screening: Participants responding to recruitment efforts (see page 36) will be screened by telephone. If participants prefer to answer some of the screening questions through the Yale Qualtrics system, participants will indicate their consent to the recruitment/screening process in the online system. Potentially eligible participants will be consented and evaluated in-person by trained doctoral clinicians. Participants will complete survey measures of eating behaviors and psychopathology and psychosocial functioning around the time of the in-person appointment.

Participants who provide informed consent and are determined to be eligible (see page 21) will then participate in the study as depicted and described in the following paragraphs. See also Figure 1 (page 8).

Baseline Assessment: As part of the determination of eligibility (for full criteria, see page 21), participants will complete two interviews, the MINI International Neuropsychiatric Interview-Version 7.0 (MINI) and Eating Disorder Examination (EDE) to generate psychiatric diagnoses and detailed current eating disorder features and diagnoses. Other measures, for safety and establishment of baseline values, will also be obtained: BMI, blood pressure, heart rate, eating behaviors and psychopathology, psychosocial functioning, metabolic measures, and perception of treatment measures.

For a full description of instruments, see “Measures,” which includes a grid depicting when each measure is administered (page 15). The baseline assessment will occur over two in-person meetings and is estimated to be take a total of 2-3 hours in-person.

Study Intervention: This study will be a **two-stage** randomized placebo-controlled trial with patients who have both BED and obesity. Throughout the study, participants and all study staff, including investigators and outcome assessors, will be blind to the pharmacotherapy treatment condition, and outcome assessors will also be blind to the behavioral treatment condition. **Stage 1** will test the effectiveness of BWL and NB medication, alone and in combination. **Stage 2** will test the effectiveness of NB

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medication for enhancing maintenance and longer-term outcomes (amongst responders). **Stage 2** will also explore whether adding CBT enhances on-going NB pharmacotherapy (amongst non-responders). See Figure 1 on page 8.

Randomization to Stage 1 Treatment: Eligible participants (determined at the end of the baseline assessment according to inclusion/exclusion criteria as described on page 21) who agree to participate and provide written informed consent will be randomized to one of the four treatments. *N*=160 patients with obesity and BED will be randomly assigned in balanced factorial (2 X 2) design, to one of four 16-week methods: BWL+NB, BWL+Placebo, NB, or Placebo.

We will use blocked randomization with random block sizes of 4 and 8 for Stage 1 to obviate any secular trends. We will monitor the randomization procedure and determine whether systematic differences in demographic characteristics (age, gender, race/ethnicity) or clinical characteristics (BMI, binge-eating frequency, psychiatric co-morbidity) become evident. We will consider adjustment to randomization if indicated (Kraemer & Fendt, 1990; Kraemer & Pruyn, 1990).

Stage 1 Treatment Protocols:

Treatment Protocol for Naltrexone/Bupropion (NB) Pharmacotherapy: Medication will be prescribed per FDA-approved guidelines for obesity and as used in previous RCTs demonstrating effectiveness of NB medication for weight loss in patients with obesity (Greenway et al., 2010; Greenway, Whitehouse, et al., 2009; Smith et al., 2013; Wadden et al., 2011). NB medication will combine naltrexone sustained-release (SR, 32 mg/day) combined with bupropion SR (360 mg/day) taken daily (8 mg naltrexone/90 mg bupropion in each tablet – two tablets taken twice daily; matching tablets and frequency for placebo).

Following regimens in previous RCTs, a dose escalation approach will be used, beginning with a quarter of the full dose and increasing weekly until the full dose is achieved at week 4 (Greenway et al., 2010; Wadden et al., 2011). This dose will continue for the remainder of the trial. If a patient develops intolerable side effects, the study physician may reduce the dose to achieve tolerability. If the patient cannot tolerate the medication, has adverse effects, or is non-compliant with medication for >7 consecutive days, s/he will be discontinued from the medication arm.

Participants will meet with the study physician at the start of treatment. The brief visit (10 minutes) will focus on compliance and evaluating side effects. Participants will meet monthly with study staff throughout Stage 1 treatment.

Treatment Protocol for Behavioral Weight Loss (BWL): The BWL treatment is a mixture of the published LEARN behavioral lifestyle weight control treatment developed by Brownell (2000) and the Diabetes Prevention Program (Knowler et al., 2002); the PI and research team has extensive experience administering BWL with patients with BED and obesity. BWL will be delivered weekly by research-clinicians according to treatment manuals that detail session-by-session procedures. These manuals closely parallel patient-version BWL self-care materials for the entire course of treatment and follow

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closely that used by Wadden et al. (2011) in the COR-BMOD Trial testing BWL and NB/placebo medication for obesity. BWL will instruct patients in developing and maintaining a balanced deficit diet comprised of roughly 20% protein, 30% max of fat, and 50% carbohydrate, with general goals of 1500kcal/day. Behavioral strategies (goal-setting, self-monitoring, stimulus control problem-solving) will be taught within a lifestyle approach for achieving dietary goals (augmented by portion size and caloric goals) and physical activity goals (to achieve 180 min/week of moderate physical activity). Research-clinicians will be trained in BWL by the research team and will be supervised and monitored over the course of treatment delivery to ensure quality adherence.

Stage 1 Post Assessment: After completing Stage 1 treatment (BWL+NB, BWL+Placebo, NB, or Placebo), participants will complete an assessment, the EDE, to assess for binge-eating episode frequency. Based on this interview, participants will be classified as "responders" (65% or greater reduction in binge-eating episodes, per findings suggesting prognostic significance of such responses) (Grilo, Masheb, & Wilson, 2006; Grilo, White, Wilson, Gueorguieva, & Masheb, 2012) or "non-responders." Other measures are described in the "Measures" grid that depicts when each measure is administered (page 15).

Randomization to Stage 2 Treatments:

"Responders" to acute treatments (65% or greater reduction in binge eating) will be randomized to NB or placebo for 16 weeks of maintenance pharmacotherapy. Participants and investigators will remain blind to pharmacotherapy condition. Randomization will occur in equal proportions using stratified blocked randomization with first treatment as a stratifying variable.

"Non-responders" will continue Stage 1 pharmacotherapy (NB/placebo) and 50% will be randomized to receive CBT (weekly for 8 weeks and biweekly for 8 weeks) in addition to continued pharmacotherapy. Participants and researchers will remain blind to pharmacotherapy condition.

"Non-responders" to Stage 1 who were not randomized to CBT in Stage 2 will be given the option of receiving CBT after Stage 2 post has been completed and before entering the follow-up stage. Participants who choose to receive CBT after Stage 2 will have an additional post-treatment assessment when they finish CBT treatment, and then will begin the follow-up stage.

The study biostatistician (Dr. Gueorguieva) will create randomization lists and communicate directly with the research pharmacist.

Stage 2 Treatment Protocols:

Treatment Protocol for Naltrexone/Bupropion (NB) Pharmacotherapy: Medication prescription and dosage will be the same as described in the NB Treatment protocol for Stage 1. Participants will meet with the study physician for a brief visit at the start of Stage 2, and will meet with study staff monthly throughout Stage 2 treatment.

"Responder" participants randomly assigned to discontinue medication will receive a one-week down-titration followed by placebo. Participants randomly assigned to continue active medication will receive the same active dose throughout Stage 2.

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Participants randomly assigned to begin NB medication in Stage 2 will receive a three-week dose escalation as previously described. The double-blind will be maintained by providing all participants with three weeks of medication in dated envelopes.

"Non-responder" participants will continue their Stage 1 NB/placebo pharmacotherapy without interruption.

After 12-month follow-up assessments are completed, patients will be informed (separately from investigators by research pharmacist) whether they were on NB or placebo. Medication double-blind will be maintained for investigators and outcome assessors until all participants have completed final 12-month follow-up assessments.

Treatment Protocol for CBT: In Stage 2 treatment, "non-responders" to Stage 1 treatments will be randomly assigned to receive CBT or not. CBT will be delivered by research-clinicians based on CBT treatment manuals (Fairburn, Marcus, & Wilson, 1993) used in our previous RCTs (Grilo, Masheb, & Salant, 2005; Grilo et al., 2011) and similar to those used in leading CBT RCTs (Wilfley et al., 2002). CBT manuals provide detailed session-by-session procedures for the clinicians and patients. CBT is a "specialist" focal treatment with three overlapping phases. (1) Establishing a collaborative therapeutic relationship while focusing on educating patients about the nature of binge eating and factors thought to maintain the problem. Specific behavioral strategies (e.g., self-monitoring) are used to help patients identify problematic eating behaviors while establishing a normal structured eating pattern. (2) Integrating cognitive restructuring procedures, focusing on helping patients learn to identify and challenge maladaptive cognitions regarding eating and weight/shape and thoughts that trigger binge eating. (3) Maintaining change and preventing relapse**.**

Stage 2 Post Assessment and Follow-up Assessments: After completing Stage 2 treatment (NB, Placebo, CBT+NB, or CBT+Placebo), participants will complete one interview, the EDE. Other measures are described in the "Measures" grid that depicts when each measure is administered (page 15).

Measures:

Figure 3. Grid depicting when each measurement is obtained

		Stage 1				Stage 2				Follow-up	
	Baseline Assessment	Mid-Treatment Week 4	Mid-Treatment Week 8	Mid-Treatment Week 12	Stage 1 Assessment (Week 16)	Mid-Treatment Week 4	Mid-Treatment Week 8	Mid-Treatment Week 12	Stage 2 Assessment (Week 16)	6 Month Follow-up	12 Month Follow-up
Clinical Interview:											
EDE Interview	*				*				*	*	*
Medical history, Start of new treatments	*				*				*		*
MINI Psychiatric Interview	*										
Self-report Questionnaires:											
EDE-Q; Godin; BDI-II	*	*	*	*	*	*	*	*	*	*	*

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TFEQ; FCI-II; PFS	*	*			*	*			*		*
YFAS, ELOCS; PPAQ; SF-12	*				*				*		*
PSQI; Audit-2; UPPS	*				*				*		
Physical Assessment:											
BMI, BP, HR	*	*	*	*	*	*	*	*	*	*	*
Liver Function	*	*			*	*					
Lipids, GC	*				*				*		*
Opiate drug testing	*										
As needed: Pregnancy testing	*										
As needed: TSH	*										
Perceptions of Treatment:											
Treatment Credibility	*	*				*					
Compliance, Adverse Events		*	*	*	*	*	*	*	*		
Placebo Rating		*			*	*			*		
Treatment Satisfaction					*				*		

Clinical Interviews:

- MINI International Neuropsychiatric Interview-Version 7.0 (**MINI**) (Sheehan et al., 1998) is a brief structured interview for Axis I psychiatric disorders. Validation and reliability studies have supported the MINI, including good convergence with SCID (Sheehan et al., 1998). The MINI requires much less time than the SCID and reduces participant burden while providing adequate psychiatric data to characterize patients and determine exclusion criteria.
- Eating Disorder Examination Interview–16th Edition (**EDE**) (Fairburn & Cooper, 1993) is an investigator-based interview assesses the features of eating disorders and generates eating disorder diagnoses. The EDE will be our primary method for assessing binge eating and eating disorder psychopathology. The EDE focuses on the previous 28 days, except for diagnostic items, which are rated for additional duration stipulations to address *DSM-5* criteria for BED. The EDE assesses the frequency of different forms of overeating, including objective binge-eating episodes (OBE; i.e., unusually large amounts of food with loss of control). The EDE also comprises four scales (dietary restraint, eating concerns, weight concern, and shape concern) and a global severity score. The EDE has good psychometric properties (Grilo, Masheb, & Wilson, 2001b), is the major outcome measure for BED RCTs (Wilfley et al., 2002; Wilson et al., 2010), and has good test-retest reliability.
- We will also gather clinical data on the patient's medical history prior to the study, which we will update as indicated in Figure 1. If patients begin other treatments, this will allow us to account for this in analyses.

Assessment Training: Independent outcomes assessors will receive training in diagnostic interviews from investigators following well-established protocols used in previous projects. Once interviewers are certified in the measures (MINI and EDE), they will receive ongoing supervision to ensure consistent use and prevent drift.

Self-Report Questionnaires:

- Eating Disorder Examination-Questionnaire Version (**EDE-Q**). The self-report EDE-Q (Fairburn & Beglin, 1994) generates the same overeating data and scale scores as the EDE interview. EDE-Q has good test-retest reliability with BED patients (Grilo, Masheb, & Wilson, 2001a; Grilo et al., 2001b; Reas, Grilo, &

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Masheb, 2006). The EDE-Q converges well with the EDE as a measure of "change" (Sysko, Walsh, & Fairburn, 2005).

- Godin Leisure Time Exercise Questionnaire (**Godin**) (Godin & Shephard, 1985) assesses frequency of mild, moderate, and vigorous physical activity. The Godin has good test-retest reliability (Godin & Shephard, 1985) and has good support from validation studies using various activity measurements such as activity monitors and maximum oxygen consumption (Miller, Freedson, & Kline, 1994).
- Beck Depression Inventory (**BDI-II**). The BDI (Beck & Steer, 1987) is a widely used measure of the symptoms of depression. A voluminous literature has documented good internal consistency (studies range .73 to .95), short-term test-retest reliability, and convergent validity (Beck, Steer, & Carbin, 1988).
- Three Factor Eating Questionnaire (**TFEQ**) (Stunkard & Messick, 1985) measures eating behaviors with 3 factors: cognitive restraint, disinhibition, and hunger. TFEQ has empirical support (Foster et al., 1998), and shows differential response across treatments consistent with putative mechanisms (Grilo & Masheb, 2005; Safer, Agras, Lowe, & Bryson, 2004).
- Food Craving Inventory (**FCI-II**) (White, Whisenhunt, Williamson, Greenway, & Netemeyer, 2002) assesses general and specific food cravings and comprises four subscales for different food groups. The FCI has been validated and psychometrically supported in studies with obesity and with obesity/BED groups (White & Grilo, 2005; White et al., 2002).
- Power of Food Scale (**PFS**) (Lowe et al., 2009) assesses the psychological impact of and the drive to consume palatable foods in an obesogenic environment. The PFS measures appetite for–rather than the consumption of–palatable foods. The PFS has been validated in large normative (Lowe et al., 2009) and obese samples including weight-loss treatment-seeking obese patients (Cappelleri et al., 2009). The PFS comprises 3 scales reflecting food proximity (food available, food present, and food tasted) supported by factor analysis and good test-retest reliability and internal consistency (range 0.81-0.91) (Cappelleri et al., 2009). The PFS is a good measure of the hedonic impact of food environment cues; fMRI studies have reported associations with state cravings for desired foods and shifts in brain networks (Rejeski et al., 2012).
- Yale Food Addiction Scale (**YFAS**) (Gearhardt, Corbin, & Brownell, 2009) is a measure of addictive eating behaviors with high fat/sugar foods. Items correspond to the substance dependence diagnostic criteria. The YFAS has demonstrated adequate internal reliability, convergent validity, and incremental validity in predicting binge eating.
- Eating Loss of Control Scale (**ELOCS**) (Blomquist et al., 2014) assesses the complexity of loss of control eating over the past four weeks. The ELOCS has demonstrated good convergent validity and is considered a valid self-report questionnaire that may provide important clinical information regarding experiences of LOC in obese persons with BED.
- Paffenbarger Physical Activity Questionnaire **(PPAQ**) (Paffenbarger, Hyde, Wing, & Hsieh, 1986) measures specific physical activity (complementing the Godin) and has been used extensively in epidemiological (Paffenbarger, Hyde, Jung, & Wing, 1984; Paffenbarger, Wing, & Hyde, 1978) and obesity treatment studies.

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PPAQ has good psychometrics (Albanes, Conway, Taylor, Moe, & Judd, 1990) and correlates significantly with expensive and burdensome fitness measures (Siconolfi, Lasater, Snow, & Carleton, 1985).

- Medical Outcomes Study Short-Form Health Survey (**SF-12**) (Ware & Sherbourne, 1992) is widely-used measure of health related quality of life. This measure has well-established reliability and validity (McHorney, Ware, Lu, & Sherbourne, 1994; McHorney, Ware, & Raczek, 1993) for physical health and mental health domains.
- Pittsburg Sleep Quality Index (**PSQI**) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a widely used measure of quality and patterns of sleep, assessing namely subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The PSQI has demonstrated good internal consistency and reliability (Cronbach's alpha = .83).
- Alcohol Use Disorders Identification Test (**AUDIT-2**) (Bohn, Babor, & Kranzler, 1995) is a measure that assesses alcohol use. The AUDIT has been used extensively and demonstrates high internal consistency and good test-retest reliability (Reinert & Allen, 2007).
- UPPS-P Impulsivity Scale (**UPPS**) (Whiteside & Lynam, 2001) measures impulsivity in five domains: negative urgency (acting rashly in response to negative emotions), positive urgency (acting rashly in response to positive emotions), lack of premeditation (acting without taking into account consequences), lack of perseverance (difficult remaining focused on difficult or boring tasks), and sensation-seeking (favoring stimulating or exciting activities) (Cyders, Littlefield, Coffey, & Karyadi, 2014).

Physical Assessment:

- Lipid profiles (**Lipids**): total cholesterol, HDL-, LDL-cholesterol, triglycerides will be obtained fasting per established protocols (Anderson et al., 1995).
- Glycemic Control (**GC**): HbA1c, Glucose and Mean Plasma Glucose, routine measures of average glucose control for a previous (3-month) period.
- Hepatic function panel (**Liver Function**) will be assessed for safety.
- Thyroid-stimulating hormone (**TSH**) will be assessed if patients report any history of thyroid disease or are taking thyroid medications.
- Urine drug testing for opiates will be assessed for all patients.
- Pregnancy testing will be assessed for female patients of child-bearing potential.

- Body Mass Index (**BMI**) will be calculated using measured Height (measured once at baseline) and Weight (obtained regularly at assessment meetings).
- Blood Pressure (**BP**) and Heart Rate (**HR**). BP readings (both systolic and diastolic) and HR will be obtained regularly at assessment meetings.

Perceptions of Treatment:

- Treatment Credibility and Satisfaction. Credibility and Satisfaction ratings will allow patients to provide feedback on the treatment and treatment delivery.

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- Treatment Compliance will include **pill count** method for medication treatment and **session attendance** as compliance measure for BWL.
- Adverse Events will be assessed using an adverse event checklist of most commonly reported adverse events for NB. Research-clinicians will ask open-ended and follow-up questions as needed.
- Placebo Ratings. Patients and clinicians will record whether they believe the patient is on active medication or placebo.

Maintenance of Cohort. Research staff will form on-going relationships and maintain contact with participants. Our experience indicates this improves likelihood of participants' willingness to perform follow-up assessments. In addition: (1) At pre-screening and baseline assessment, participants will be asked whether they will be available for the entire study duration; (2) Participants will be excluded if unable to comply with birth control methods; (3) Participants will provide names and contact information of at least two relatives or friends and permission to contact them if they move without notifying investigators; (4) At each assessment, participants will be asked if they have plans to move; and (5) We will reimburse participants for completion of the assessments.

D. 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

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

One hundred sixty (*N*=160) participants with obesity and binge-eating disorder, and meeting other eligibility criteria as described below, will be randomized to participate

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in this trial. Previous work with this population suggests participants will be adults, male and female, and represent diverse racial/ethnic and sociodemographic groups.

F. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment 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	
☒ **N/A**		

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)

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

Participants will be recruited using the same broad advertisements as in our previous RCTs (see page 36). Potential participants will be screened by telephone (or, if preferred by the participant, through the Yale Qualtrics system) and potentially eligible patients will be consented and evaluated in-person by trained doctoral clinicians.

Inclusion Criteria:

(1) 18 to 70 years old;
(2) Meet DSM-5 criteria for BED based on semi-structured diagnostic interview (EDE);
(3) BMI 27-30 with a controlled obesity-related co-morbidity; or BMI ≥ 30 and <50;
(4) Available for the duration of the treatment and follow-up (20 months).
(5) Read, comprehend, and write English at a sufficient level to complete study-related materials.

Exclusion criteria:

Main exclusion criteria reflect primarily clinical or medical issues that would indicate different treatment needs or contraindication to NB medication.

(1) Predisposition to seizures (e.g., history or evidence of seizure disorder, febrile seizures during childhood, brain tumor, cerebrovascular disease, or significant head trauma; family history of idiopathic seizure disorder, or is currently being treated with medications or treatment regimens that lower seizure threshold).
(2) Lifetime anorexia or bulimia nervosa, or currently regularly self-inducing vomiting.
(3) Currently taking MAOI medication, or history of hypersensitivity.

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(4) Currently taking opioid pain medications or drugs.
(5) Positive urine drug screen for opiates.
(6) Currently using effective medications for weight loss.
(7) History of allergy or sensitivity to bupropion or naltrexone.
(8) Co-existing psychiatric condition that requires hospitalization or more intensive treatment (e.g., bipolar mood disorders, psychotic illnesses, severe depression).
(9) Untreated hypertension with a seated systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg, or heart rate > 100 beats/minute.
(10) History of congenital heart disease, cardiovascular disease, cardiac arrhythmias requiring medication, atherosclerotic disease, or a history of cerebrovascular pathology including stroke.
(11) Current uncontrolled Type I or Type II diabetes mellitus.
(12) Untreated hypothyroidism with a TSH > 1.5 times the upper limit of normal for the test laboratory.
(13) Gallbladder disease.
(14) History of severe renal, hepatic, neurological, chronic pulmonary disease, or any other serious, unstable medical disorder.
(15) Current or recent (within 12 months) drug or alcohol dependence
(16) Currently receiving effective treatment for eating or weight loss.
(17) Currently participating in another clinical study in which the participant is or will be exposed to an investigational or a non-investigational drug or device.
(18) Breast-feeding or pregnant, or not using a reliable form of birth control.
(19) Reports active suicidal or homicidal ideation.

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

Diagnostic Assessment. Participants will be interviewed by trained and supervised doctoral-level research-clinicians (MINI and EDE) to determine whether they meet criteria for binge-eating disorder. These diagnostic clinical interviews will also determine whether participants have any co-existing psychiatric conditions (including substance use disorders) that require hospitalization or more intensive/different treatment.

Physical Assessment. The study physician will determine medical eligibility based on results of participants' physical examination (within one year of starting the study), and/or approval of participant's primary care provider, as well as results of the baseline assessment. Information obtained from the physical examination will include a list of current medications, which participants will be asked to bring to their baseline assessment.

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

NB Pharmacotherapy.

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Since participants will undergo a thorough physical evaluation and screening for known contraindications for treatment with the NB medication, potential risks will be minimized. In clinical trials, NB was associated with the following side effects in 10% or more of the time and significantly greater than rate in placebo: nausea, headache, constipation, and vomiting. NB was associated with the following side effects less than 10% of cases but significantly more than placebo: dizziness, insomnia, dry mouth, and diarrhea. Large studies (e.g., Greenway et al., 2010 with N=1742) reported that the proportion of participants reporting a serious adverse event did not differ between NB and placebo (1.6% versus 1.4%) and that none of the observed events were judged to be related to the study. It appears important to evaluate and monitor blood pressure and heart rate because studies have found that patients with obesity treated with NB have significantly lower drops than placebo in systolic BP changes (-0.4 vs. -2.1), diastolic BP (-0.1 vs -1.0), pulse rate (1.0 vs -0.1) (Greenway et al., 2010).

Pill Placebo.

The main risk associated with placebo is failure to improve, although some persons do improve solely on placebo. Although the placebo is inactive, some persons who take the placebo report that they experience some of the side-effects listed above. Participants will have a 50% chance (by random) of receiving placebo instead of NB during Stage 1. Since participants have a 50% chance of receiving BWL at the first stage of treatment, there is a 25% chance (by random) overall of receiving only placebo. Since participants have a 50% of receiving CBT in the second stage (if they are non-responders), the chances of receiving only placebo drop to roughly 12.5%. Additionally, “non-responders” to Stage 1 who were not randomized to CBT in Stage 2 will be given the option of receiving CBT after Stage 2 post has been completed.

Assessments, Interviews, and Behavioral Treatment.

BWL is an established and widely-used standard obesity treatment. CBT is an established “specialist” treatment for BED (considered the leading treatment by various research guidelines). Neither BWL nor CBT have any meaningful risks. With BWL, the only foreseeable risks include some mild discomfort or embarrassment when discussing eating patterns and weight. Some mild hunger may be experienced initially when attempting to follow the modest caloric guidelines. Some mild fatigue may be experienced initially when attempting to increase modest lifestyle physical activity. With CBT, the only foreseeable risks include some mild discomfort or embarrassment when discussing binge eating, body image, and associated thoughts and feelings. Previous controlled clinical trials with similar interventions with large numbers of similar patients have not reported problems. Any troublesome effects would be readily identifiable by the experienced research clinicians during the repeated evaluations.

Research assessments are all noninvasive, and should add no substantial risk. The major disadvantages are the time taken to complete them and possible breach of

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confidentiality. Our past experience with these measures indicates that they are acceptable to participants. Careful efforts aimed at maintaining confidentiality will be made. All identifiable information will be stored in a locked research cabinet. All participants will be assigned a study participant number. Subsequently, participants will be identified only by that number and an encoded version of their initials (e.g., John Smith = JSMI). A list of numbers and the corresponding names will be maintained by the Principal Investigator and stored in a locked research cabinet. Any identifying information that is collected will be kept in a locked research cabinet in a locked unit. Any information published as a result of the study will be such that it will not permit identification of any participant. All information collected will remain confidential except when we are legally required to disclose such information by law. These circumstances include knowledge of abuse of a child or elderly person, threats of harm to self or others, and plans to harm to property. Data will be stored in locked cabinets for 7 years after the final data are collected. Research records may be the subject of an audit by a regulatory agency within the federal government. Organizations which have a responsibility for protecting human subjects, including the Yale IRB (Human Investigation Committee), may have access to the research records. Additionally, the funding agency (NIH) may have access to the research records. The participant's identity will remain protected except as required for legal or regulatory inquiries. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996. All research personnel will be trained on IRB, ethics, and HIPAA procedures.

There is the possibility that drawing blood might cause a small bruise, mild discomfort, or infection.

Failure to Improve. There is a chance that the patient's binge eating or obesity may fail to improve or may worsen during the study.

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

Effective screening will exclude all prospective participants who would be at greater risk for complications because of medical or psychiatric illnesses. Participants will be evaluated repeatedly throughout the study and will be monitored for any adverse reactions. Given the uncertain effects of medication during pregnancy, the following precautions will be taken for women of reproductive age: 1) a female participant of reproductive age will be asked to have a pregnancy test, 2) a female participant of reproductive age must agree to use a reliable method of birth control while she is in the study and to alert the research team if she departs from her birth control plans or if, in spite of adherence to these plans, she thinks she might be pregnant; we will do a pregnancy test as needed during the treatment phase of the study,, and 2) if a woman becomes pregnant after study entry, her medication will be discontinued.

Wallet Safety Card. Each participant will be given a wallet card with the code number for the medication assignment in the event of an emergency and the need

for breaking the blind. The research pharmacy has 24-hour service. Participants will be provided with contact information for the study physician and the PI, as well as emergency numbers in case of adverse events or other concerns.

Warning about Opioid Withdrawal: We will include this advisory pertaining to opioid use and examples of opioid-based medications and drugs in the written consent form, verbal consent process, and on the wallet card: *Naltrexone can cause withdrawal symptoms in individuals who are taking opioid pain medications or drugs. You should not participate and we will not include you in the study if we know or suspect you are using opiate-containing drugs.*

Urine drug screen for opiates: Participants will be asked to have a urine drug screen for opiates. Participants with a true positive test for opiates will be excluded, per exclusion criteria.

Monitoring of Depressive Symptoms. To monitor changes in depressive symptoms, patients will be asked to complete the BDI-II at monthly clinic visits. Research clinicians will review BDIs during the clinic visit, and if indicated, will asked pointed questions pertaining to suicidality. If the research clinician judges that the participant is experiencing significant adverse effects of the medication, the investigators and study physician will be consulted to determine whether to discontinue the medication. The participant will be compensated in full, and will be asked to continue to attend clinic visits and to continue to participate (if applicable) in the BWL/CBT treatment to ensure remission of any distressing symptoms. If warranted, the participant will be given a referral. In addition, the following advisory will be included in the verbal consent process, and written on the consent form: *The U.S. Food and Drug Administration (FDA) has issued an Advisory cautioning health care providers, patients, and families to closely watch individuals taking naltrexone/bupropion medication for signs of their depression getting worse and for thoughts of killing or harming themselves, especially during the first several weeks that the medication is being taken. Patients and their families should watch for and promptly report new symptoms. For example, report to the study doctor as soon as possible any signs of impulsivity (taking action or saying something without thinking first), agitation (feeling nervous or finding sitting still very difficult), and panic attacks (extreme fear without apparent reason).*

Blood pressure and heart rate will be measured during all evaluation visits. Two readings will be taken at each assessment. In the event of high systolic blood pressure, diastolic blood pressure, or heart rate, the study physician will be notified and will determine whether additional intervention and/or medication discontinuation is warranted.

Liver function will be measured during baseline and month-1 clinic visits of Stage 1 and Stage 2. The study physician will review results. Participants with hepatic disease will be excluded if this is detected at baseline, per exclusion criteria. The

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study physician will determine whether changes or out-of-range values require additional intervention and/or medication discontinuation.

Medication Titration. Participants will have a three-week dose escalation as previously described: one tablet daily (Naltrexone 8mg/ Bupropion 90mg; 1 week), two tablets daily (Naltrexone 16mg/ Bupropion 180mg; 1 week), three tablets daily (Naltrexone 24mg/ Bupropion 270mg; 1 week), followed by the full dose for the remainder of treatment.

If participants drop out of the study during either treatment phase, we will ask that they return any unused medication. Participants who have been on the study medication for more than 4 weeks, including those who complete the treatment, will be asked to taper off the study medication: two tablets daily (Naltrexone 16mg/ Bupropion 180mg; 4 days), then one tablet daily (Naltrexone 8mg/ Bupropion 90mg; 3 days), to discontinue medications. Participants on placebo will take the same number of tablets as the active group to maintain the blind. Participants will be cautioned against stopping the medication abruptly. Taper off is not medically necessary for participants on the study medication for 4 weeks or less.

K. **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?
   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. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
      i. Minimal risk
      ii. Greater than minimal
   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?

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews monthly. During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB, the study physician or the research safety monitor (Cenk Tek, MD) has the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with the NB combination medication as minimal risks.
2. Given the now established safety and validity of the current NB combination medication in RCTs and FDA approval, we do not view the proposed studies as high risk.

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 or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

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

Serious Adverse Events:
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 results in any of the following outcomes:

1. Death;
2. A life-threatening experience requiring in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

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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. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the participant population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented***.***

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol, including the study physician and the protocol's research safety monitor, Cenk Tek, MD.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
□ National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
□ Study Sponsor
□ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

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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. The principal investigator will review all adverse events upon completion of every study subject.

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

Baseline demographic and clinical characteristics for [redacted] groups will be compared using chi-square tests for categorical variables, ANOVA or Kruskal-Wallis tests for continuous variables. Continuous variables will be examined for adherence to normal distribution using normal probability plots and Kolmogorov-Smirnov tests. If normality is not satisfied and transformations do not help with achieving normality, alternative analytic strategies will be considered such as generalized estimating equations or nonparametric methods. Dropouts and completers will also be compared. Analyses will be intent-to-treat. Primary outcomes will be tested at the two-sided 0.05 significance level. Secondary analyses will be adjusted for multiple tests using Bonferroni correction.

Overall analysis strategy: Mixed-effects models (Diggle, Heagerty, Liang, & Zeger, 2002) will be used to compare treatments. These models allow for different numbers of observations per participant, use all available data on each participant, and are unaffected by randomly missing data. A further advantage is the capacity to test and account for individual-difference contributions to the treatment outcomes (Cudeck, 1996; Cudeck & Klebe, 2002; Hedeker et al., 1996; Hedeker & Gibbons, 1996; Singer, 1998). They provide flexibility in modeling the correlation structure of the data. In models for each outcome, we will include fixed effects of time, BWL, NB and all possible interactions, and random participant-level effects. Because we cannot a priori predict the shape of the response over time in each arm of the trial we will first treat time as a categorical predictor and will then test for polynomial trends over time. We will consider different error structures (e.g., AR1, independence) and select the best fitting one based on information criteria. We will compare dropout patterns between groups and if there are concerns of informative dropout or informative intermittent missing data, we will use pattern mixture models (Hedeker & Gibbons, 1997) to perform sensitivity analyses.

Stage 1 RCT – Primary Aim #1: Test effectiveness of BWL and NB medication, alone and in combination, for BED. The primary aims are to evaluate the effectiveness for (a) reducing binge eating and (b) reducing weight. In the mixed models, the dependent variables will be (a) reduction in binge eating frequency, and (b) Percent weight loss. In view of the factorial design we will also be able to assess whether there are interactive or additive effects of the two treatments. We do not have a priori hypothesis regarding the interaction but will test it together with the main effects.

Stage 1 RCT – Secondary Aims: (a) Explore effectiveness of BWL and NB medication, alone and in combination, on secondary outcomes: remission (zero binges past 28 days), eating-disorder pathology (EDE global), and depression (BDI). To compare remission rates across groups we will use logistic regression with BWL, NB

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and the interaction as fixed effects. We will also test the interaction of the two treatments. Continuous secondary outcomes (EDE global and BDI) will be analyzed using the same approach as for primary aim 1. (b) Explore predictors, moderators, and mediators of primary outcomes (binge eating and weight loss). We will follow Kraemer's (2002) conceptual/statistical models for exploring predictors, moderators and mediators for both binge eating and % weight loss outcomes. Per Kraemer (2002), we will explore if baseline characteristics predict/moderate treatment effects by testing for main effects and interactions in models specified above for primary outcomes. In terms of mediators, we will explore whether differential symptom changes during treatment are associated with subsequent longer-term primary outcomes. Repeated assessments of eating behaviors (EDEQ and TFEQ scales) and physical activity (Godin, PPAQ) constructs relevant to BWL, food-reward constructs (FCI, PFS) relevant to putative mechanisms of action for NB, and depression (BDI) a conceptual/empirically-supported construct, will yield relevant change variables for analyses of mediation (i.e. testing subsequent changes in binge eating and weight).

Stage 2 RCT – Primary Aim # 2: Among responders to Stage 1 treatments, to evaluate the effectiveness for (a) binge eating and (b) weight. Our main hypothesis is that NB will have main effects on reduced binge eating and weight regains. In the mixed models for testing these hypotheses, the dependent variables will be (a) change in binge eating frequency and (b) percent weight change.

Stage 2 RCT – Secondary Aims: (a) Among responders, explore effectiveness of NB medication vs. placebo on secondary outcomes: relapse to BED threshold (binge once weekly), eating-disorder pathology (EDE global), depression (BDI), social/medical functioning (SF-36), and metabolic function (Lipid, Hb1Ac). Relapse rates across groups will be compared with logistic regression with medication as a fixed effect. Continuous secondary outcomes (EDE global and BDI) will be analyzed using the same approach as for primary aim 1. (b) Explore whether Stage 1 treatment is a moderator of medication effects during Stage 2. To test this hypothesis we will include treatment during phase 1 and its interaction with medication in models above. We will estimate effect sizes for outcomes.

Stage 2 RCT – Exploratory Aim: Among Non-responders to Stage 1, we will explore whether adding CBT enhances on-going pharmacotherapy (NB/placebo). We will compare CBT plus continued pharmacotherapy vs pharmacotherapy-only for reducing binge eating.

Power analysis: The sample size was based on the following power calculations.

Stage 1 RCT – Primary Aim #1: Reported effect sizes for naltrexone/bupropion effects on dimensional weight loss (% weight loss) are large (d=0.76 in Apovian et al (2013), d=0.98 in Greenway et al. (2013), and d=1.1 in Smith et al. (2013). However, because of the possibility of positive publication bias and since medium effect sizes (d=0.5) or larger are also considered clinically meaningful, we conservatively power our study to detect medium effect sizes. With 40 participants in each cell of the design table, we will

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have at least 80% power to detect such effect sizes (d=0.5, f=0.25) for the medication main effects at 2-sided significance level of 0.05 even after accounting for 20% dropout. With the sample sizes per group we are also well powered (power > 80%) to detect clinically meaningful effect sizes (f=0.25) for the interaction test between BWL and NB on percent weight loss even after assuming 20% dropout. Dropout rate is based on completion rates for our earlier RCTs with BED (87% in Grilo & Masheb, 2005; 84% in Grilo, White et al., 2014).

Stage 1 RCT – Secondary Aims: Remission rates for BWL for BED from our previous RCTs were 50% (Grilo & White, 2013) and 74%; Wilson, Wilfley et al. (2010) reported 55% remission rate for BWL for BED. Thus, we conservatively calculate power based on estimated 50% remission rate for BWL alone. Remission rates for no-BWL/placebo are estimated at 10-15% (based on McElroy (2015) placebo rates in 2 large RCTs of 14% and 13%). We estimated remission rate for NB medication at 45% (synergistic action of NB medication expected to produce higher rate than the 42% rate for bupropion-only (White & Grilo, 2013) and expect higher remission rate for the combination BWL/NB of 60%-70%. This results in the following projected effect sizes for the main effects of BWL (55% vs 28%, 60% vs 30%) and NB (53% vs 30%, 58% vs 33%). With sample size of 40 in each cell, we have more than 80% power to detect such differences assuming 2-tailed tests, alpha=0.05, with 20% dropout.

Stage 2 RCT*:* Based on our previous RCTs, we anticipate 70% of participants on BWL+NB and 65% on BWL or on NB will be responders. This yields a sample size of 88 participants (28 on BWL+NB, 26 on BWL, 26 on NB, and 8 on placebo) for randomization to Stage 2 NB or placebo. Thus, if we base power calculation for phase 2 on 44 participants per group and account for 20% dropout, we have at least 80% power to detect a medium to large effect size (d=0.68) for the difference between NB vs placebo at 2-tailed alpha of 0.05. For relapse, we can detect the following clinically meaningful differences in proportions (15% vs 45%, 30% vs 63%, 45% vs 77%) at 2-tailed alpha of 0.05.

Stage 2 RCT – Exploratory Aim*:* With N=72 non-responders (N=36 assigned to continuing medication (NB/placebo) and N=36 assigned to CBT plus continuing medication (NB/placebo), we would have 80% power to detect d=0.75 (remission rates of 5% vs 32%, 15% vs 49%, 30% vs 66%) at 2-tailed alpha level of 0.05 assuming up to 20% dropout.

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

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

A. DRUGS, BIOLOGICS and RADIOTRACERS

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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).

In September 2014, the FDA approved ("Contrave") the combination of naltrexone and bupropion to treat obesity consisting of the following empirical support from several RCTs performed with obesity (but not BED). NB medication will combine naltrexone sustained-release (SR, 32 mg/day) combined with bupropion SR (360 mg/day) taken daily (8 mg naltrexone/90 mg bupropion in each tablet – two tablets taken twice daily; matching tablets and frequency for placebo).

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: ☒ **N/A**

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?

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)

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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.

NB Pharmacotherapy. An FDA-approved anti-obesity pharmacotherapy approach involves the *combination* of naltrexone and bupropion which has received empirical support in several RCTs performed with obesity (non-BED).

Mechanisms of Action. The putative mechanisms of action for NB seem relevant for binge eating in addition to weight loss. **Naltrexone**, an opioid receptor antagonist, is approved to treat alcohol and opioid dependence (O'Malley et al., 2007). Naltrexone produces weight loss in lab animals but only minimal weight losses in people (Billes & Greenway, 2011; Malcolm et al., 1985). **Bupropion** operates through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms (Han, Hwang, & Renshaw, 2010; Slemmer, Martin, & Damaj, 2000; Stahl et al., 2004). Bupropion may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and

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reduced weight gain during smoking cessation (Farley, Hajek, Lycett, & Aveyard, 2012; Hurt et al., 1997). Bupropion promotes weight loss (Li et al., 2005): in a meta-analysis of five trials of bupropion, the mean difference in weight loss was 2.77 kg (CI, 1.1 to 4.5) between bupropion and placebo groups at 6 months. White and Grilo (2013) reported preliminary, modest support for weight loss specifically in patients with obesity and BED.

NB Combination. The putative mechanisms of action for NB is especially relevant for reducing binge eating and weight per hypothesized effects on brain regions implicated in the regulation of food intake and weight based on research on the mechanisms of action of leptin (Billes & Greenway, 2011). The anorectic effects of leptin result from its excitatory effects on pro-opiomelanocorin (POMC) neurons in the hypothalamus melancortin system (Cowley et al., 2001; Marsh et al., 1999). Stimulated POMC signaling decreases food intake, increases energy expenditure, but is then inhibited by endogenous feedback (Cowley et al., 2001). Thus, combining these two drugs will stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) (Billes & Greenway, 2011; Greenway, Whitehouse, et al., 2009). This synergistic model received support both in vitro and in vivo studies (Cone et al., 2001; Greenway, Whitehouse, et al., 2009).

Obesity Outcomes. Recently, several large RCTs have reported that the combination of these two medications (Naltrexone/Bupropion) were effective in promoting weight loss in obese patients (Greenway et al., 2010; Greenway, Whitehouse, et al., 2009; Smith et al., 2013; Wadden et al., 2011). These RCTs reported significant clinically-meaningful weight losses with sustained-release naltrexone (32 mg/day) plus sustained-release bupropion (360 mg/day) combined in fixed-dose tablets. Most recently, Apovian et al. (2013), in a study of 1496 obese patients reported significantly greater weight losses relative to placebo (-6.5% vs -1.9% at week 28 and -6.4% vs -1.2% at week 56) and significantly greater likelihood of achieving 5% weight loss (56% vs 18% at 28 weeks and 51% vs 17% at 56 weeks). These findings supporting NB medication are quite consistent with earlier (large) RCTs which reported the following percentage of patients achieving at least 5% weight loss: 56% vs. 18% (Smith et al., 2013); 52% vs. 15% (Greenway, Dunayevich, et al., 2009). *Thus, the proposed RCT study will test the effectiveness of Naltrexone/Bupropion relative to placebo for reducing binge-eating and producing weight loss in obese patients with BED.*

Risks. Several large-scale studies have found that this medication is safe and effective for the treatment of obesity (Greenway et al., 2010; Greenway, Whitehouse, et al., 2009; Smith et al., 2013; Wadden et al., 2011). The NB combination approved by the FDA (Contrave) is reported to have the following common adverse reactions: nausea (32.5%), constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%). In addition, Contrave will have the FDA warnings and precautions: “Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Contrave if symptoms develop. Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding coadministration with high-fat meal. Increase in Blood Pressure and Heart Rate: Monitor blood pressure and heart rate in all patients, especially those with cardiac or

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cerebrovascular disease. Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction observed with naltrexone exposure. Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. Use of Antidiabetic Medications: Weight loss may cause hypoglycemia. Monitor blood glucose."

3. **Source:** a) Identify the source of the drug or biologic to be used.
   NB will be purchased using funds awarded in this grant.

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

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

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.

   Expert opinion (Wilson et al., 2007) and critical quantitative meta-analytic reviews (National Institutes of Clinical Excellence, 2004) conclude CBT is the best-established treatment for BED; CBT, however, does not produce clinically meaningful weight loss and is not readily available given the need for specialized training. Alternative therapies include other psychological therapies such as interpersonal psychotherapy (which also fails to produce weight loss and is not readily available since it requires intensive training and few practitioners employ it) and self-help versions of CBT (which will be used in this study). Alternative pharmacologic therapies include antidepressant medications (SSRIs) although weight loss is uncertain with those agents.

   Pharmacotherapy (medications) for BED has received increased research attention albeit nearly all RCTs have been of short duration and without follow-up period to establish durability (Reas & Grilo, 2008, 2014). Critical review and meta-analysis show that several drugs – working through varied mechanisms – have short-term efficacy relative to placebo for reducing binge-eating and produce weight

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loss ranging from modest to none (Reas & Grilo, 2008). Placebo-controlled trials of anticonvulsants topiramate and zonisamide (Claudino et al., 2007; McElroy et al., 2003; McElroy et al., 2006) have reported effects for reducing both binge-eating and weight (with a mean improvement in weight loss of approximately 3-4 kg compared to placebo), but have also shown frequent dropout and adverse events which become nearly universal with longer use (McElroy et al., 2004). SSRI antidepressants, previously regarded as a potential treatment strategy (National Institutes of Clinical Excellence, 2004) are characterized by small effect sizes relative to placebo (Reas & Grilo, 2008) and produce no weight loss at all (Grilo, Masheb, & Salant, 2005) and are inferior to CBT (Grilo, Masheb, & Wilson, 2005; Ricca et al., 2001). There are currently no FDA-approved medications for BED.

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

Participants may receive placebo medication for up to 8 months if randomized to placebo during both Stage 1 and Stage 2 of this study

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

Without immediate effective treatment, the greatest potential harm is that binge eating and associated eating disorder features may not improve. Placebo-controlled trials have rarely reported worsening and generally report a positive placebo response (Reas & Grilo, 2014).

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

Possible risks include failure of binge eating and associated eating disorder features to improve. Previous experience suggests that the frequency of these situations is rare (Reas & Grilo, 2014).

To safeguard participants, we plan to assess potential adverse events, side effects, and clinical status. All participants will have monthly visits with research clinicians, who can be expected to detect the clinical changes that warrant concern. Participants will be removed from the study if, through the consultation of the PI and study physician, it is determined that participant safety is at risk, including worsening depression, suicidal ideation, intensification of binge eating, or failure to comply with medication. If a participant is removed from the study, a research clinician will provide referrals. If removal is indicated, a referral for appropriate care will be provided.

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*.

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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.

Our procedure follows existing pharmacotherapy treatment literature for BED, which has delivered medications in an acute, short-term manner.

B. DEVICES ☒ **N/A**

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol N=160
   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 ☒	☒ Billboards
☒ YCCI Recruitment database		
☒ Other (describe): EPIC direct to patient	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	

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

Participants will be recruited using ads and flyers placed in local media (newspapers and television), and internet and printed materials throughout the community. We will also work with YCCI using their recruitment strategies, including distribution of materials throughout the community, email

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and internet solicitation, working with community contacts, and receiving information about potential participants YCCI identified as interested in research related to our topics (obesity, binge eating disorder, mental and physical health).

EPIC Direct to Patient MyChart confidential messaging will be utilized for recruitment of subjects meeting specific parameters (Adults meeting weight inclusion criteria who are not on anti-depressant medication, using other exclusion criteria to refine sample to those likely eligible). The following template will be utilized:

Title of study, Phase or type of study: Behavioral and Pharmacologic Treatment of Binge Eating and Obesity

Principal Investigator: Carlos Grilo, Ph.D.

Study Contact: Janet Lydecker, Ph.D. Phone # 203-785-7210

Description:
If you are 18 to 70 years old with binge-eating disorder and obesity, and are not taking anti-depressant medications, you may be eligible to participate in a free and confidential study that may help with long-lasting weight loss. **No cost treatment** provided (FDA-approved medication, behavioral, or both). Participants will receive up to $400 compensation. To learn more or see if you are eligible to participate, please call the Yale Program for Obesity, Weight, and Eating Research at: (203) 785-7210 or visit http://psychiatry.yale.edu/research/programs/clinical_people/power.aspx.

Please indicate how often you would like to receive new names of potential participants ☐ daily ☒ weekly

b. Describe how potential subjects are contacted.

Advertisements will ask participants to contact our research team if they are interested in the study. When potential participants call and/or respond to an online form, they will be screened to determine whether they are likely to be eligible. If they seem potentially eligible and interested, they will be scheduled for an initial assessment.

c. Who is recruiting potential subjects?

After initial contact, research clinicians (who have completed IRB training) will meet with potential participants to discuss the study, the treatments, the assessments, the follow-up period, and the informed consent procedures and

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forms. Clinicians will answer any questions and obtain written informed consent. A copy of the signed informed consent form will be given to the participants and the original will be kept in the participant's file. All potential subjects and/or participating participants are free to decide whether or not to participate and are free to withdraw from the study at any time. Alternative treatments would be discussed and/or referrals provided. A decision not to participate or to discontinue participation would not adversely affect future interactions with Yale or the Yale School of Medicine.

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:

☒ 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?

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

If yes, describe the nature of this relationship.

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
   ☐ For inclusion of non-English speaking subject if short form is being used

   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;

   Participants will initially call us and/or fill out an online interest form in response to advertisements, at which time, if they seem eligible, we will schedule them for an initial assessment and collect contact information. We will also request that patients complete online surveys. If potential participants elect to participate, they would then provide informed consent including HIPAA authorization as described at their initial in-person visit. Names will be removed from surveys if an individual does not provide informed consent.

   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

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

List of Investigators / Study Personnel:

Person Name	Department	Lead Unit	Role	Consenting
Grilo, Carlos M	• MPSY O S A Y P I	☑	Principal Investigator	Yes
Barnes, Rachel			Personnel	Yes
Bartel, Maya			Study Personnel	Yes
Cooper, Zafra			Personnel	No
Gueorguieva, Ralitza			Personnel	No
Ivezaj, Valentina			Personnel	Yes
Leiner, Emily Isadora			Personnel	Yes
Lydecker, Janet			Personnel	Yes
Massoumi, Mehran M			Personnel	Yes
Morgan, Peter Thomas			Personnel	Yes
O'Brien, Elizabeth			Study Personnel	No
Rasmusson, Grace Elizabeth			Study Personnel	Yes
Tsopelas, Lindsay Mariel			Study Personnel	Yes
Wang, Shirley			Study Personnel	No
Warren, Justine Ilia			Personnel	Yes
White, Marney A.			Personnel	No

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.

   At the start of the initial intake evaluation, participants will provide written consent to participate in a research project and treatment. Informed consent will be collected at 301 Cedar Street. Clinicians will answer any questions that participants may have. Alternative treatments would be discussed and/or referrals provided. Participants will be informed that a decision to not participate or to discontinue participation would not adversely affect future interactions with Yale or the Yale School of Medicine. Participants also will be informed that their participation is strictly voluntary, and that they may withdraw at any time with no penalty.

10. **Evaluation 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.
    With all participants, we will describe the study verbally during the consent process, and allow participants to ask any questions they might have. To ensure understanding, we will use open-ended questions with all participants to ask that they paraphrase the nature of the research and what they are being asked to do as part of the study, and also summarize the potential risks and benefits of the study.

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.

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The Compound Authorization Form is attached.

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use. ☒ **N/A**

12(a) As a limited alternative to the above requirement, will you use the short form for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?*
YES ☐ NO ☐

Note If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.*

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. Please review the guidance and presentation on use of the short form available on the HRPP website.

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

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

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

AND

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

☐ **Requesting a waiver of signed consent for the <u>Entire Study</u> (**Note that an information sheet may be required.)
If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research? ☐ *Yes* ☐ *No*
b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ *Yes* ☐ *No*

OR

c. Does the research pose greater than minimal risk? ☐ *Yes If you answered yes, stop. A waiver cannot be granted.* ☐ *No*
AND
d. Does the research include any activities that would require signed consent in a non-research context? ☐ *Yes* ☐ *No*

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

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

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

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

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☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

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?

Height, weight, medical and psychosocial history will be collected and used for research.

Lab results (bloodwork and urine tests), including urine drug screen for opiates, will be collected and used for research.

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

All participants will be assigned a study number. Subsequently, participants will be identified only by that number. A list of numbers and the corresponding names will be maintained by investigators on a protected research server. Any identifying information that is collected on paper will be kept in locked research cabinets within a locked suite. Interviews will be recorded using a digital recorder and recordings will be securely and separately stored and be identified only by a study number and date.

Any information published as a result of the study will be such that it will not permit identification of any participant. All information collected will remain confidential except when we are legally required to disclose such information by law. These circumstances include knowledge of abuse of a child or elderly person, threats of harm to self or others, and plans to harm to property.

Information about positive urine drug screens, should they occur, will be recorded using the participant study number. Results from drug screens that are conducted alongside bloodwork and therefore have identifiable data will be retained for the duration of the study and maintained on secure Yale servers (for electronic data) or in locked research cabinets within a locked suite. We will destroy positive urine drug test results that occur alongside identifiable information as soon as the participants is determined to be ineligible.

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

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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?

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

See above, the patients will only be identified by a number on any digital data files. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996.

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.

Data will continue to be stored in locked cabinets in limited access areas until the legal requirement for storage has been met. Electronic data files will be password protected. Electronic data files will include code numbers only – i.e., will not contain patient identifying information.

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)

The PI and research staff will have access to the PHI. Research records may be the subject of an audit by a regulatory agency within the federal government. Organizations which have a responsibility for protecting human participants, including the Yale Human Investigation Committee (HIC), may have access to the research records. The participant's identity will remain protected except as required for legal or regulatory inquiries. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996.

g. If appropriate, has a Certificate of Confidentiality been obtained? ☒ **N/A**

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

No, this is unlikely.

SECTION IX: POTENTIAL BENEFITS

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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.)

Participation in the study has the potential to result in decreased frequency of binge eating and weight loss for at least some patients through free assessments and treatment. More generally, the low risk is offset by the potential of identifying effective behavioral and pharmacological treatments for reducing binge eating and weight in obese persons with binge eating disorder, which would be beneficial to many persons who experience these conditions.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

   Alternatives include community referrals for cognitive behavioral therapy, behavioral weight loss, or medications.

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.

		Stage 1				Stage 2				Follow-up	
	Baseline Assessment	Mid-Treatment Week 4	Mid-Treatment Week 8	Mid-Treatment Week 12	Stage 1 Assessment (Week 16)	Mid-Treatment Week 4	Mid-Treatment Week 8	Mid-Treatment Week 12	Stage 2 Assessment (Week 16)	6 Month Follow-up	12 Month Follow-up
Payment for Participation	$20				$100				$100*	$80	$100

Participants will be reimbursed when they complete the assessments at baseline ($20), and at the end of Stage 1 ($100), Stage 2 ($100), 6-Month Follow-up ($80), and 12-Month Follow-up ($100). At baseline, conditions for receiving compensation include attending the appointment. At subsequent assessments, conditions for receiving compensation include completion of surveys, bloodwork, and interview.

*A minority of patients (estimated to be 5% of all participants) will have the option to receive CBT after Stage 2 before completing follow-up assessments (See page **Randomization to Stage 2 Treatments:**
14). These patients will be asked to complete an additional assessment (prior to the follow-up stage) and will therefore receive an additional $100 at the time of that assessment. Conditions for receiving compensation include completion of interview, surveys, and bloodwork.

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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.

   Psychological assessment, labwork, and treatment will be provided at no cost to participants, their insurance, health plan benefits nor other third party payer. Participants will be asked to provide information from a recent (within one year) physical with their primary healthcare provider. If they have not had a physical within the past year, we will ask them to obtain a physical prior to participating in the study. A physical exam with their own primary healthcare provider would be at the participant's (or the participant's insurance) cost. (Note: In research we have conducted in the past with patients diagnosed with binge eating disorder, the majority of patients had a physical within the past year.)

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. Referrals for treatment will be made.

   b. Where and from whom may treatment be obtained?

   If the participant is injured as a direct result of participation in this research study, the medical staff at the Yale-New Haven Hospital would be available to provide immediate emergency care, short-term hospitalization and/or short-term outpatient care.

   c. Are there any limits to the treatment being provided?

   If the participant is injured as a direct result of participation in this research study, the treatment will be determined by the medical provider(s).

   d. Who will pay for this treatment?

   The participant or participant's insurance carrier will be billed for the cost of this treatment. There are no plans to compensate the participant for physical or mental disability, lost wages, or any other losses or damages occurring over the long term or if an injury becomes apparent after participation in the study has ended. However, by agreeing to participate in this research study, the participant is not waiving or giving up any legal rights to seek compensation. Participants who believe they have been injured should contact the Principal Investigator, Dr. Carlos Grilo at 203-785-2792 immediately.

   e. How will the medical treatment be accessed by subjects?

   Referrals will be provided.

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