



IRB: 2000029057

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Pharmacological and Behavioral Treatments to Treat Loss-of-Control Eating and Improve Weight Outcomes after Bariatric Surgery

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(If applicable) **Clinicaltrials.gov Registration #:** NCT04599478, NCT04605081, and NCT04599504

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.
2. If a section or question does not apply to your research study, type “Not Applicable” underneath.
3. Once completed, upload your protocol in the “Basic Information” screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **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 RCT to test the effectiveness of BWL and pharmacologic treatments, alone and in combination, for the treatment of loss-of-control (LOC)-eating following metabolic and bariatric surgery (MBS). The first stage RCT will provide new findings regarding the effectiveness of behavioral weight loss (BWL) and of Naltrexone/Bupropion (NB) medication (FDA-approved for weight-loss) and whether this specific combination of behavioral and pharmacologic treatments is effective for patients who have regular LOC-eating and obesity following MBS. Findings from the COR-BMOD Trial [Wadden et al., 2011] provided support for the efficacy of combining NB pharmacotherapy with BWL for obesity. No such study has been performed with patients following MBS. The second stage RCT will provide new and novel findings from a controlled test, amongst Responders to Stage 1 treatments, whether NB medication results in superior maintenance and longer-term outcomes than placebo. The second stage RCT will also explore, in double-blind fashion, amongst Non-responders to Stage 1 treatments, whether switching to an alternative (distinct) medication (lisdexamfetamine; LDX), a recently FDA-approved medication for binge-eating disorder, results in clinical improvements.

Stage 1 (Initial Randomization). N=160 patients with obesity and regular LOC-eating following MBS will be randomly assigned (double-blind) in a balanced factorial (2 X 2) design, to one of four 16-week interventions: BWL+NB, BWL+Placebo, NB, or Placebo. The randomization will be in equal proportions but stratified by surgery type.

Stage 2 (Response-based Randomize). “*Responders*” to Stage 1 treatments will be randomized (double-blind) in equal proportions (stratified blocked randomization with first treatment as stratifying variable) to NB or placebo for 12 weeks. “*Non-responders*” to Stage 1 will be randomized (double-blind) to a different medication (LDX or placebo).

Independent (blinded) assessments will occur through 12-month follow-up (i.e., 19 months total).

- (1) **Stage 1 RCT – Primary Aim:** *Test* effectiveness of BWL and NB medication, alone and combined, for LOC-eating post-MBS for (a) reducing LOC-eating and (b) enhancing weight-loss.
- (2) **Stage 2 RCT – Secondary Aim:** Among *Responders* to Stage 1 acute treatments, *examine* the effectiveness of NB medication relative to placebo for enhancing maintenance and longer-term outcomes.
- (3) **Stage 2 RCT – Exploratory Aim:** *Explore*, *amongst Non-responders* to acute treatments, whether a second alternative (distinct) medication enhances outcomes (reduces LOC-eating).

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

December 1, 2020- November 30, 2027

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

Major Public Health Significance. Obesity is one of the world’s major public health problems. Individuals with obesity suffer from increased risk of cardiovascular morbidity and mortality [Benjamin et al., 2018; Khan et al., 2018], as well as type 2 diabetes, obstructive sleep apnea, dyslipidemias, asthma, and several cancers [Guh et al., 2009; Martin-Rodriguez et al., 2015]. Rates of obesity (defined as body mass index (BMI) ≥ 30) have steadily

increased over the last few decades to a staggering 39.8% [Hales, Fryar & Ogden, 2017]. Obesity prevalence in the general adult population is expected to rise to over 51%, with a 130% increase in severe obesity (BMI ≥ 40) by 2030 [Sturm & Hattori, 2013; Finkelstein et al., 2012]. These rates and projections are deeply concerning given the substantial disease and economic burden of obesity [Whitlock et al., 2009; Andreyeva, Sturm & Ringel, 2004]. As severe obesity rates continue to rapidly rise, the use of metabolic and bariatric surgeries (MBS) is expected to increase [Nguyen et al., 2011].

MBS Effectiveness. MBS is the most effective and enduring treatment for severe obesity and results in impressive acute and long-term weight loss and improvement and/or remission of medical comorbidities [Sjostrom, 2013; Sjostrom et al., 2007, 2004] and psychosocial sequelae [Kontinen et al., 2015]. The Swedish Obese Subjects (SOS) study found significantly greater weight loss with MBS than the non-surgical control group that was treated conventionally [Sjostrom, 2013]. Specifically, 2 years after surgery, MBS lost -23% of their starting weight versus 0% for the control group and 20 years after treatment, MBS lost -18% versus -1% for the control group [Sjostrom, 2013]. In addition to impressive weight loss, MBS reduces mortality and produces significant reductions in adverse cardiovascular events relative to standard care [Sjostrom et al., 2012]. Currently, laparoscopic Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) are the most commonly performed MBS procedures in the US [Spaniolas et al., 2015; Nguyen et al., 2013]. RYGB usually results in >50% excess weight loss [Buchwald et al., 2004], and improvements or amelioration of medical comorbidities including diabetes, hypertension and dyslipidemias [Sjostrom, 2013; Sjostrom et al., 2004]. LSG utilization rates recently surpassed RYGB rates [Spaniolas et al., 2015], in part due to relatively comparable (albeit slightly less) weight loss, the relative ease of performing the operation, and fewer acute complications than RYGB [Carlin et al., 2013]. Both LSG and RYGB far surpass weight loss outcomes achieved by the laparoscopic adjustable gastric band [Carlin et al., 2013], which has been largely abandoned in the US [Spaniolas et al., 2015].

Marked MBS Outcome Heterogeneity. Despite overall impressive MBS outcomes [Courcoulas et al., 2013; Courcoulas et al., 2017], weight outcomes are markedly variable after MBS and weight regain with reoccurrence of medical comorbidities is common, suggesting that MBS alone is often not enough. While overall mean improvements are impressive, inspection of weight outcomes reveals marked heterogeneity following both RYGB and LSG. As depicted in **Figure 1**, lowest maximal weight loss was as low as -1.1% for LSG and -4.1% for RYGB, with ranges of 1.1-58.3% for LSG and 4.1-60.9% for RYGB [Manning et al., 2015]. As shown in **Figure 2** below, even for those with optimal outcomes, weight regain after MBS is associated strongly with worsening or recurrence of medical comorbidities, and is therefore of great concern [Courcoulas et al., 2017; King et al., 2019].

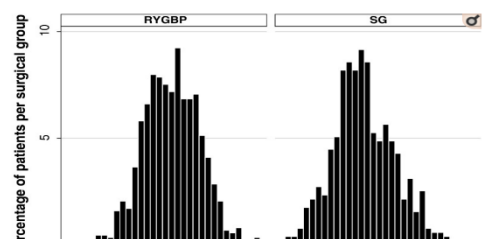


Figure 1. Weight variability after MBS^[22]

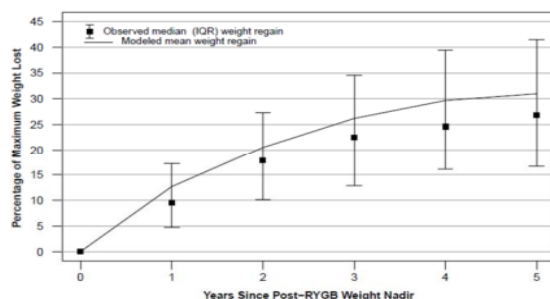
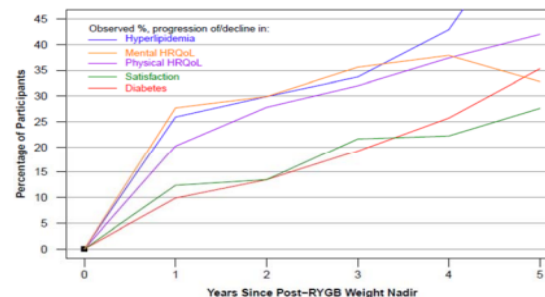


Figure 2. Weight Regain After MBS^[24]



Increased Clinical Outcomes Associated with Regain ^[24]

Predicting Poor MBS Outcomes. Given concerns about durability of MBS outcomes and particularly the heterogeneity of MBS weight outcomes, a substantial body of research has attempted to identify *pre-surgical* predictors. Research has examined a broad range of pre-surgical patient variables but *has failed to identify any reliable pre-surgery predictors* of weight loss or functioning following bariatric surgery. *For example, the investigative team* performed a series of studies documenting that MBS candidates' weight loss goals [White et al., 2007], binge eating [White et al., 2006], sexual abuse histories [Grilo et al., 2006], body-image disturbance [Hrabosky et al., 2006], and depression [Masheb et al., 2007] did *not* represent negative prognostic predictors for RYGB outcomes. Our team's findings are consistent with the majority of the available literature, *including the rigorous NIDDK-funded LABS 2 and 3 studies* [King et al., 2019; Devlin et al., 2016; Devlin et al., 2018; Kalarchian et al., 2019; Kalarchian et al., 2016], which have ***not identified reliable modifiable pre-surgery patient predictors*** of MBS outcomes [White et al., 2006; Herpertz et al., 2004; van Hout, Verschure & van Heck, 2005; Burgmer et al., 2005; Kinzl et al., 2006; Sockalingam et al., 2017; Latner et al., 2004; Meany, Conceicao & Mitchell, 2014; Powers et al., 1999; White et al., 2010].

Post-surgical Loss-of-Control (LOC) Eating Reliably Predicts Outcomes. In contrast to the lack of reliable pre-surgical predictors of outcomes, **research has identified one reliable post-surgery predictor of subsequent outcomes - "loss of control" (LOC) eating** [White et al., 2010; Colles, Dixon & O'Brien, 2008; de Zwaan et al., 2010; Kalarchian et al., 2002; Kruseman et al., 2010; Rusch & Andris, 2007]. It is increasingly recognized (including by the **ICD-11**) that the subjective sense of "loss of control" is the core or essential component of "binge eating." Research with diverse clinical and community samples across all weight levels has consistently found that it is the "loss of control" that is clinically meaningful (regardless of quantity of food consumed) and is a potent predictor of both associated eating-disorder psychopathology and psychological disturbance [Latner et al., 2004; Elder et al., 2008; Mond et al., 2010; Goldschmidt, 2017], a distinction that has increasingly been recognized in the MBS literature [Devlin et al., 2018; Meany, Conceicao & Mitchell, 2014; White et al., 2010; de Zwaan et al., 2010; Kalarchian et al., 2002; Ivezaj et al., 2017; Ivezaj et al., 2018; Smith et al., 2019].

Clinically, we emphasize that following MBS, binge eating – defined traditionally by unusually large quantity of food – is physically difficult and, if it occurs, typically results in significant distress (e.g., dumping syndrome). In contrast, eating smaller quantities of food while experiencing "loss of control" [Mond et al., 2010] remains possible. Indeed, studies have reported that roughly one-third to one-half of patients report regular episodes of **LOC** post-surgery [Devlin et al., 2018; White et al., 2010; Kalarchian et al., 2002; Kruseman et al., 2010] and predict significantly poorer weight loss, weight regain, and psychosocial functioning [King et al., 2019; Devlin et al., 2018; Meany, Conceicao & Mitchell, 2014; White et al., 2010; Colles, Dixon & O'Brien, 2008; de Zwaan et al., 2010; Kalarchian et al., 2002; Kruseman et al., 2010; Rusch & Andris, 2007]. The LABS consortium found that post-MBS binge-eating disorder (BED), which involves LOC eating as the salient feature, was the only psychiatric predictor of poorer weight outcomes [Kalarchian et al., 2016]. Thus, post-surgery LOC – (not requiring "unusually large amount" as in "binge eating") – is a reliable predictor for poorer longer-term outcomes and an ideal marker for identifying patients in need of postsurgical clinical intervention.

Post-MBS Treatment Research is Needed. Despite the chronicity of obesity, established evidence-based obesity treatments to enhance or augment MBS outcomes do not exist. Although the field increasingly recognizes the need for post-operative treatments to address the *marked heterogeneity of outcomes in general* and to address the *specific needs of those with LOC-eating in particular*, *there is virtually no empirically-informed guidance available*. A review follows of potential relevant behavioral and pharmacologic interventions from the obesity and BED fields.

Behavioral Treatment. Of the very limited research to date which has examined pre- and post-MBS interventions to improve weight outcomes, results suggest that pre-surgical interventions have largely been ineffective at producing significant weight differences post-surgically [Kalarchian et al., 2013; Kimpuri et al.,

2018]. Conversely, post-surgical interventions have been associated with improved weight outcomes; yet, the quality of the available studies is considered to be methodologically poor and limited by, for example, lack of randomization, high attrition, and small samples. Specifically, Beck et al. [2012] rated rigor of post-MBS treatment studies using Jadad criteria (range “0” signified low quality to “5” signified high quality). The average Jadad score was only 0.6 with 5/9 studies rated “0” and 4/9 rated “1”, signifying very low quality and rigor.

A systematic review suggested that post-surgery behavioral treatments might have some utility [Stewart & Avenell, 2016]. A search of the literature for post-MBS randomized controlled trials (RCTs) directly targeting weight loss (n=7) [Nijamkin et al., 2012; Papalazarou et al., 2010; Kalarchian et al., 2012; Sarwer et al., 2012; Tucker et al., 1991], revealed very few studies; overall, results were mixed with less than half reporting significant differences [Nijamkin et al., 2012; Papalazarou et al., 2010; Kalarchian et al., 2012]; although of the various interventions, behavioral treatments performed best for weight outcomes. Nonetheless, most RCTs had small sample sizes (i.e., N=18 [Chacko et al., 2016]) or studied various forms of low-intensity methods, such as text messaging [Lauti et al., 2018], which clearly do not represent the strongest or most effective weight-loss treatment from the obesity literature being tested for patients after MBS. More rigorous RCTs involving behavioral weight loss (BWL) are clearly needed. This gap is even more striking for behavioral interventions to address LOC eating post-MBS. To date, three small pilot studies (single-arm) [Bradley et al., 2017; Sockalingam et al., 2019; Himes et al., 2015] and one small controlled pilot study [Weineland et al., 2012; Weineland, Hayes & Dahl, 2012] testing various treatments (e.g., “acceptance commitment therapy,” “standard of care,” dialectical behavior therapy”) have found that LOC (“subjective binge eating”) eating frequency decreased with the interventions post-MBS.

The investigative team performed the only NIH-funded RCT testing different manualized behavioral interventions for LOC-eating following MBS. The findings (see Preliminary Findings) demonstrate feasibility of recruiting and treating post-MBS patients with LOC-eating but point to need for more intensive methods. Specifically, it is logical that intensive BWL – which our investigative team has demonstrated strong and durable outcomes (both for eliminating LOC eating and for reducing weight) for patients with “full-threshold” BED with comorbid obesity [Grilo et al., 2011; Grilo, White, Masheb, Ivezaj, Morgan & Gueorguieva] – would have clear potential utility for addressing LOC-eating post-MBS. As reviewed critically [Grilo, 2017; Hilbert et al., 2019], an alternative “specialist” CBT treatment reliably reduces binge-eating (LOC-eating) but fails to produce weight loss, as we have demonstrated [Grilo et al., 2011]. Thus, BWL seems logical for MBS.

Pharmacologic Treatment. Another very promising, yet remarkably understudied, avenue involves the use of specific medications after MBS. While emerging research suggests there might be utility in using weight-loss medications after MBS [Schwartz et al., 2016; Stanford et al., 2017; Hanipah et al., 2018], these findings must be interpreted with great caution given the studies’ significant methodological limitations. Specifically, *existing studies on post-MBS medication have used retrospective designs and lacked appropriate controls*. In fact, no RCT has tested the effectiveness of pharmacotherapy after MBS for either weight-loss or for disordered eating [Hanipah et al., 2018; Gutt et al., 2019].

Which Weight-Loss Medication? Although several different (FDA-approved) weight-loss agents could potentially be used to augment weight outcomes after MBS, one in particular seems conceptually most relevant given its potential mechanistic action and effects on disordered eating behaviors such as LOC-eating. The combination of Naltrexone and Bupropion (NB), also known as Contrave, is an optimal starting point due to its consistent weight-loss evidence base, affordable cost of generics, tolerable side-effects, safety profile, and putative mechanisms of action. Specifically, in 2014, the FDA approved NB for obesity following empirical support from several RCTs performed with obesity [Greenway et al., 2009; Greenway, Fujioka & Plodkowski, 2010; 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 pills. These

findings supporting NB medication are quite consistent with earlier large RCTs which reported greater weight loss with NB than placebo (-6.5 vs -1.2% [Greenway, Fujioka & Plodkowski, 2010]; -8.2% vs -2.1% [Smith et al., 2013]).

Putative mechanisms of action for NB seem relevant for post-MBS patients struggling with LOC eating and may also enhance weight loss. Naltrexone, an opioid receptor antagonist, is approved for treatment of alcohol and opioid dependence [O'Malley et al., 2007]. Naltrexone alone produces weight loss in lab animals but only minimal weight losses in humans [Malcolm et al., 1985; Billes & Greenway, 2011]. Bupropion alone, thought to operate through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms [Slemmer, Martin & Damaj, 2000; Stahl et al., 2004; Han, Hwang & Renshaw, 2010], may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and reduced weight gain during smoking cessation [Hurt et al., 1997; Farley et al., 2012]. Bupropion has been found to promote weight loss in obesity. White & Grilo [2013] first reported preliminary support for a possible (albeit modest) weight loss benefit specifically in patients with obesity and BED. Putative mechanisms of action for the combination NB is especially relevant for reducing LOC eating and weight per hypothesized effects on brain regions implicated in the regulation of food intake and weight based on the mechanisms of action of leptin [Billes & Greenway, 2011]. Leptin's anorectic effects result from its excitatory effects on pro-opiomelanocortin (POMC) neurons in hypothalamus melanocortin 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 stimulates POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) [Greenway et al., 2009; Billes & Greenway, 2011].

What If First Medication (or BWL) Do Not Work: What Alternative for Non-Responders?

There is a pressing need for more complex models of care to find ways to improve outcomes. Adaptive treatment strategies have been proposed for chronic diseases [Lavori & Dawson, 2007] such as obesity [Almirall et al., 2014]. These remain conceptual models [Almirall et al., 2012] and in need of empirical evaluation. Adaptive approaches propose that initial responses to treatments inform subsequent treatments and there are emerging examples in addressing disordered-eating [Grilo, White, Masheb, Ivezaj, Morgan, Gueorguieva; Chen et al., 2017]. Perhaps most simply, if a particular treatment works (e.g., BWL and/or NB medication), does maintenance treatment enhance longer-term outcomes? The obvious second question is if the particular treatment fails to work, would a second "alternative" medication (ideally one that works via different mechanisms) perhaps help?

FDA-Approved lisdexamfetamine dimesylate (LDX) for BED. A logical alternative for treating LOC-eating might be a medication with demonstrated efficacy for BED, which is defined by the cardinal feature of LOC eating. The FDA approved (2015) *lisdexamfetamine dimesylate* (LDX) for the treatment of BED based on findings from a series of studies funded by Shire. A phase II (11-week) RCT showed that 50mg and 70mg were superior to placebo [McElroy et al., 2015]. Two identically designed phase III RCTs testing LDX (50–70 mg dose optimization) for BED [Chen et al., 2017] found LDX superior to placebo 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 11 weeks of treatment. Primary analyses of reduction in binge-eating frequency significantly favored LDX over placebo in both phase-III RCTs, with effect-size of 0.83 and 0.97 [McElroy et al., 2016]. Another smaller RCT with N=50, also funded by Shire, reported weaker advantage of LDX over placebo (ES = 0.50), suggesting the need for continued investigation by other researchers. The efficacy and safety data were reviewed and represent a favorable benefit-to-risk ratio [Citrome, 2015].

LDX was also associated with significant acute weight loss relative to placebo (mean 4.9 kg) [McElroy et al., 2015, 2016]; weight loss was examined as a safety measure. The FDA-approval and manufacturer product labeling include a "Limitation of Use" *highlighting that LDX is not indicated for weight loss* (because other CNS stimulant medications for weight loss have been associated with cardiovascular problems and the safety and efficacy of LDX for obesity remains uncertain). In the present study, we anticipate that LDX will produce short-term weight loss *and the novel, albeit exploratory, research goals will include the longer-term follow-up.*

More recently, two Shire-funded studies have *provided further support for the proposed research*. A Phase III open-label 12-month extension safety and tolerability trial of LDX for BED with N=604 patients who completed previous Shire RCTs [McElroy et al., 2015, 2016] was completed [Gasior et al., 2017]. Gasior et al [2017] reported the safety/tolerability profile with 12-months of LDX was consistent with short-term (12-week) BED trials and with established profile of LDX for ADHD (FDA-approved); 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation. Hudson et al [2017], in a double-blind RCT, reported LDX was significantly superior to placebo for preventing relapse following clinical response to open-label LDX (3.7% vs 32.1% relapsed, respectively). Hudson et al [2017] did not report follow-up data after discontinuing maintenance treatment.

Putative mechanisms of action for LDX. LDX (l-lysine-dextroamphetamine), a prodrug of d-amphetamine covalently linked to l-lysine, that when metabolized to d-amphetamine (active form) is a *moderately potent inhibitor of DAT, NET, and VMAT2*, with little affinity for SERT; *its net effect is increased catecholamine availability* [Guerdjikova et al., 2016; Hutson, Pennick & Secker, 2014; Pennick, 2010; Comiral et al., 2016]. LDX seems relevant for reducing binge-eating per preclinical and clinical [Vickers et al., 2015; Wang et al., 2011], and neurobiological (fMRI) findings suggestive that binge-eating is related to dysfunctions in the dopamine and norepinephrine systems [Balodis, Grilo & Potenza, 2015; Balodis et al., 2013], which play important roles in *regulating eating behaviors and reward* [Wellman, 2005; Palmiter, 2007].

Collectively, the lack of evidence-based treatments after MBS remains a critical gap in the severe obesity field. Both patients and health care providers are without empirical evidence to guide care after MBS; this is most concerning when patients struggle with LOC-eating. The proposed study will test the effectiveness of behavioral weight loss (BWL) and pharmacologic treatment with NB, alone and in combination, for reducing both LOC-eating and weight. Amongst Responders to the acute treatments, the study will examine the effectiveness of NB medication relative to placebo for enhancing maintenance and longer-term outcomes. Amongst Non-responders to the initial treatments, the study will explore whether a second alternative (mechanistically distinct) LDX medication enhances outcomes.

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

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 pages 35-36) 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 or remotely by trained supervised research clinicians (doctoral level and/or advanced trainees).

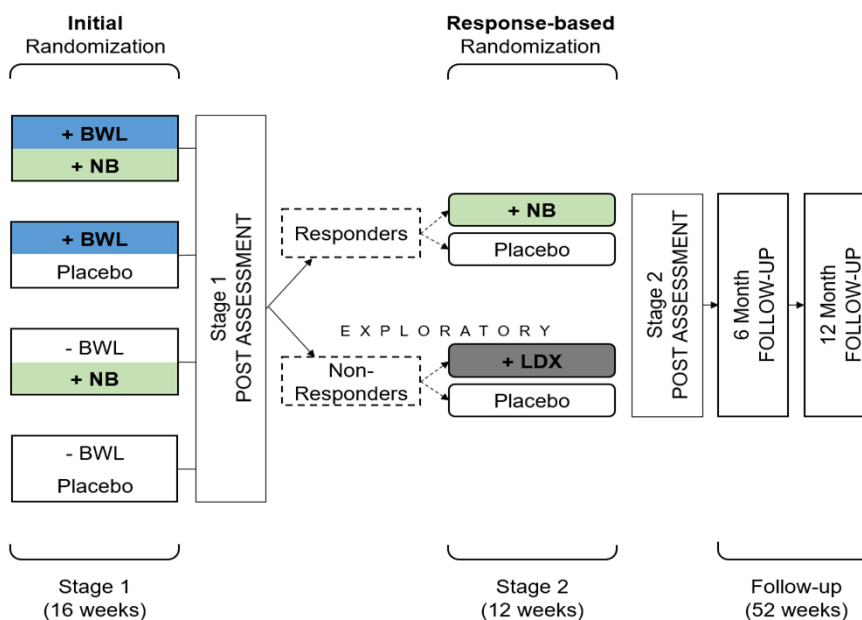
Participants who provide informed consent and are determined to be eligible (see page 21-22) will then participate in the study as depicted and described in the following paragraphs. See also Figure 3 below.

Stage 1, N=160 patients with obesity and regular LOC-eating following MBS will be randomly assigned (double-blind) in a balanced factorial (2 X 2) design, to one of four 16-week interventions: BWL+NB, BWL+Placebo, NB, or Placebo. The randomization will be in equal proportions but stratified by surgery type.

In Stage 2, “**Responders**” to Stage 1 treatments will be randomized (double-blind) in equal proportions (stratified blocked randomization with first treatment as stratifying variable) to NB or placebo for 12 weeks. “**Non-responders**” to Stage 1 will be randomized (double-blind) to a different medication (LDX or placebo).

Independent assessments will determine outcomes after discontinuation of treatments through 19 months. Secondary aims are to produce important new data regarding predictors of outcomes and moderators of treatment effects to inform prescription and exploration of potential mediators through which the distinct treatments achieve outcomes.

Figure 3. Study design



Potential participants will be screened by telephone and potentially eligible patients will be consented and evaluated in-person or remotely (e.g., via zoom) by trained supervised research clinicians (doctoral level and/or advanced trainees). (see page 36).

Randomization to Stage 1 Treatment. Eligible participants who provide written informed consent will be randomized in equal proportions to one of four treatments (using blocked randomization with random block sizes of 4 and 8 for Stage 1 to obviate any secular trends: surgery type will be a stratifying variable).

Participants will be randomized to either BWL or not, and active or inactive medication, for 16 weeks (i.e., 4 months).

Randomization to Stage 2 Treatments “Responders”.

“Responders” to Stage 1 treatments will be defined as less than once weekly LOC eating frequency during last 28 days assessed post-treatment. This rationale is based on the DSM5 and ICD-11 cutpoints of once-weekly LOC. Moreover, using data from our previous NIDDK-funded RCT for post-MBS patients with LOC (N=140), we found that patients with less than once-weekly LOC eating at post-treatment had significantly lower eating-disorder psychopathology (partial eta squared = 0.121) and lower depression (partial eta squared = 0.182) at 12-month follow-ups than patients with more than once-weekly LOC. These prospective predictive findings support this definition of “response” as less than once weekly LOC eating. “Responders” will be randomized in equal proportions (using stratified blocked randomization with Stage 1 treatment as a stratifying variable) to NB or placebo (double-blind) for 12 weeks (i.e., 3 months).

BWL Treatment Protocol. 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, obesity, and histories of bariatric surgery. 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 closely that used by Wadden et al. (2011) in the COR-BMOD Trial testing BWL and NB/placebo medication for obesity, but modified for post-bariatric surgery patients. 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.

NB Pharmacotherapy (Stage 1) Treatment Protocol. Participants will be randomized in double-blind fashion to NB or placebo. Patients and study staff, physicians and investigators will be blind to medication assignment. NB medication will comprise naltrexone (50 mg/day) combined with bupropion (300 mg/day) taken daily (matching frequency for placebo). In a previously conducted pilot study, the NB final dosage consisted of 50 mg/day naltrexone combined with 300 mg/day bupropion XL, which closely approximates the newly approved NB combination (Contrave) dosage for weight loss [Greenway et al., 2009; Greenway, Fujioka & Plodkowski, 2010; Smith et al., 2013; Wadden et al., 2011], but with advantages. One advantage is the formulations of both medications used in this study are already available generically at substantially lower cost than Contrave (75% savings for retail purchase) and the smaller size of pills (in blinding) is better for patients following MBS. Importantly, the immediate release (IR) version of Bupropion will be used in the present study as recommended by clinical guidelines for MBS populations. Because MBS can lead to changes in medication absorption due to alterations of gut anatomy, clinical practice guidelines recommend avoiding extended-release formulations of medications and using immediate release formulations (de Sousa Prado Geraldo et al., 2014; Lorico, 2020, Vouri et al., 2021). Additionally, using normal-release naltrexone rather than the sustained release formulation available only in Contrave is not seen as a pharmacokinetic disadvantage in any way. Despite a short initial serum half-life, the pharmacologic activity of naltrexone is long-lived, with an effective half-life of over 3 days, consistent with the terminal phase of plasma clearance [Lee et al., 1988]. For this reason, naltrexone has been used effectively in clinical treatment using daily or less frequent dosing. In the proposed RCT, our dosage follows standard and long-standing dosage for both naltrexone and bupropion used for related

psychiatric problems and is consistent with our previous RCT for bupropion for BED [White & Grilo, 2013] and the combination of NB for BED and obesity. Per previous RCTs, a dosing escalation approach will be used [Greenway, Fujioka & Plodkowski, 2010; Wadden et al., 2011]. This dosing will continue for the remainder of the RCT unless a patient develops intolerable side effects. If such occur, the physician may reduce the dosing to achieve tolerability. If the patient cannot tolerate the medication, has adverse effects, or is non-compliant with medication for >7 consecutive days, they will be discontinued from the medication arm. Physician visits will be brief (10 -15 minutes), focusing on compliance with dosing and evaluating side effects. For participants taking medication for greater than 4 weeks, a 7-day taper will be provided.

Study Day	Active Group		Placebo Group	
	<i>Naltrexone Capsule</i>	<i>Bupropion IR Capsule</i>	<i>Naltrexone Capsule</i>	<i>Bupropion IR Capsule</i>
1 to 7	Placebo once a day	150 mg once a day	Placebo once a day	Placebo once a day
8 to study end	50 mg once a day	150 mg twice a day	Placebo once a day	Placebo twice a day

NB Pharmacotherapy (Stage 2) Treatment Protocol: 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 the active 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. Participants randomly assigned to begin NB medication in Stage 2 will receive a dose escalation as previously described. The double-blind will be maintained. The pharmacist will maintain the blind during the bridge week between Stage 1 and Stage 2. Participants on active medication in Stage 1 who are re-randomized to active medication in Stage 2 will continue the active medication during the bridge week. Participants with active medication in Stage 1 who are re-randomized to placebo (inactive medication) in Stage 2 will down-titrate during the bridge week.

LDX Pharmacotherapy (Stage 2) Treatment Protocol. Non-responders to Stage 1 will be randomized in double-blind fashion to LDX or placebo. **LDX, FDA-approved for BED,** will be prescribed per procedures found to be superior to placebo in two large-scale phase 3 RCTs [McElroy et al., 2015]. The LDX (dose-optimization at 50-70mg per day) protocol followed the McElroy et al [2015] RCT findings that 50-70mg/day dosing was significantly superior to 30mg/dosing and to placebo. During week 1, LDX will be 30 mg/day for initial titration. During week 2, LDX will be titrated to 50mg/day. During weeks 3-4, LDX increases to 70mg will be made based on acceptable tolerability and clinical need. If 70mg is not tolerated, downward titration to 50mg/day can occur. For the remaining treatment (weeks 4-12), the optimized LDX dose (50 or 70 mg/day) will be maintained. Participants will be instructed to take the medication daily at approximately 7:00am. Safety and tolerability will be assessed during study clinic visits as will clinical compliance with the study medication. During the dose-optimization period, if the patient develops tolerability concerns, dosing can be reduced once 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. Physician visits will be brief (10-15 minutes) and focus on compliance with dosing and evaluating side effects without integrating dietary or behavioral techniques.

Withdrawal From Treatment and Other Treatments. *Withdrawal/attrition from treatments will be examined.* Use of other treatments during the study will be assessed and considered in analyses. Patients will be asked about all forms of treatments during major assessments. Criteria for removal of patients from the study may include worsening depression, suicidal ideation, intensification of loss-of-control, or failure to comply with medication. Previous experience suggests that worsening clinical status is rare; in such cases, Dr. Grilo and study physician would determine whether to remove the person from the study and provide referrals.

Maintenance of Cohort. Research staff will form on-going relationships and maintain contact with subjects. Our experience indicates this improves likelihood of participants' willingness to perform follow-up assessments. In addition: (1) At baseline, participants will be interviewed to determine 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 requested funds in the budget to reimburse participants for completion of the assessments.

Assessment Procedures. Figure 4 (p. 12) shows the assessment schedule and measures. Major assessment at: baseline, during Stage 1 treatment (month 1, 2, 3), post-Stage 1 treatment (month 4), during Stage 2 treatment (month 5, 6), post-Stage 2 treatment (month 7), and follow-ups at 6- and 12-months after completing Stage 2 treatment (i.e., 19 months after starting treatment). Outcomes assessments will be done by independent evaluators not involved in the treatment delivery and blind to treatment assignments. Participants will be asked to complete self-report surveys described below in the assessment grid. Participants will be asked permission to record sessions for training purposes and treatment fidelity. Recording is completely voluntary and refusal to grant permission to record will not influence study eligibility. Participants who agree to recordings will be asked to sign the recording section of the consent form.

Assessment Training. Independent assessors will receive training in diagnostic interviews from investigators following established protocols. Interviewers, once certified, will receive ongoing supervision to ensure consistent use and prevent drift. Dr. Grilo will do inter-rater reliability studies, which he has published for BED (Grilo et al., 2004) and psychiatry (Zanarini et al., 2000).

Eligibility and Baseline Assessment. Potential subjects will be assessed by clinicians who describe the treatment study and procedures, and obtain informed consent. Baseline assessment (up to two meetings) will include two interviews, the MINI (Sheehan et al., 2014) and EDE (Fairburn et al., 1993) modified for bariatric surgery patients, to generate lifetime and current psychiatric diagnoses and detailed current eating disorder features.

Assessment of Treatment Outcome and Time Course.

Primary Measures:

- (1) Loss-of-control eating frequency (EDE-BSV);
- (2) percent total weight loss (%TWL) using measured weight.

Secondary Measures:

(a) Cardiovascular Risk Factors/Metabolic Measures

1) Lipid profiles, HbA1c, Insulin, Glucose (measured by bloodwork); 2) Blood Pressure and Heart Rate, and 3) Neck circumference (2 and 3 measured by standard guidelines at all assessments [Abbasi, 2017])

(b) Psychosocial/Behavioral Functioning

1) Eating-disorder psychopathology (EDE-BSV); 2) Food craving (FCI); Power of food (PFS)
3) Depressive symptomatology (PHQ-9); 4) Physical Activity (GPAQ); and 5) Quality-of-life (SF-12). At baseline, informed consent will be obtained after complete description of the study to participants. Following informed consent, two semi-structured interviews will be administered, followed by self-report questionnaires.

Figure 4. Grid depicting when each measurement is obtained

Assessment Points	BASELINE	STAGE 1 DURING RX 1-MONTH	STAGE 1 DURING RX 2-MONTH	STAGE 1 DURING RX 3- MONTH	STAGE 1 POST RX 4-MONTH	STAGE 2 DURING RX 5-MONTH	STAGE 2 DURING RX 6-MONTH	STAGE 2 POST RX 7-MONTH	6-MO AND 12-MO FOLLOW-UP
Medical History, Height, MINI, Demographics CBC	•								
EDE-BSV Interview	•				•			•	•
Lipid Profile, HbA1C, Glucose, Insulin	•				•			•	•
EDE-Q-I, FCI, PFS, SF-12, PHQ-9, GPAQ, Weight, Blood Pressure, Heart Rate, Neck Circ	•	•	•	•	•	•	•	•	•
Liver Function (for safety)	•	•			•	•		•	
Adverse Events Compliance, Placebo Rating	•	•	•	•	•	•	•	•	
AUDIT, DAST	•	•			•	•		•	

Interviews:

- **Eating Disorder Examination Interview – Bariatric Surgery Version (EDE-BSV).** The EDE [Fairburn, Cooper & O'Connor, 2008] is an investigator-based interview which assesses eating-disorder behavior and psychopathology and generates eating-disorder diagnoses. The EDE will be the primary method for assessing LOC eating, as well as severity of eating-disorder psychopathology which is captured by a global severity score. *The EDE will be our primary method for assessing LOC eating and eating-disorder psychopathology at baseline, post-treatments, and follow-up assessments.* The EDE focuses on the prior 28 days, except for diagnostic items, which are rated for additional duration stipulations to address *DSM-5* criteria. The EDE has good psychometric properties [Grilo, Masheb & Wilson, 2001, 2001] and has *good test-retest reliability* in obesity groups [Grilo et al., 2004; Grilo, Lozano & Elder, 2005]. The EDE was modified for bariatric patients (EDE-BSV) and used in the NIH/NIDDK-funded Longitudinal Assessment of Bariatric Surgery (LABS) study [Devlin et al., 2016; de Zwaan et al., 2010; Mitchell et al., 2012]. The EDE-

BSV includes the original EDE questions and differentiates disordered eating from surgery-related features.

- **Mini International Neuropsychiatric Interview-Version 7.0 (MINI)** [Sheehan et al., 1998] is a brief structured interview for 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 subject burden while providing adequate psychiatric data to characterize patients and determine exclusion criteria. We will use the MINI-7 (based on *DSM-5*).

Anthropometrics:

- **Weight** will be measured on a high capacity digital scale with subjects wearing light clothing.
- **Height** will be measured to the nearest 0.1cm. Height and Weight will be used to calculate BMI, which will be used to characterize the participant study group.
- **Neck Circumference** will be measured instead of waist circumference because waist circumference may be difficult to measure reliably after MBS given the significant shape changes that occur post-MBS. Neck circumference is easier to measure, has similar or better associations with metabolic measures, and is strongly associated with waist circumference [Joshipura et al., 2016]. Finally, there are *several* different ways to measure waist circumference, none of which have been reliably tested after MBS.

Self-Report Measures:

- **Demographics:** ethnicity/race, age, sex, education, and socio-economic status.
- **Eating Disorder Examination-Questionnaire Version with Instructions (EDE-Q-I).** The self-report EDE-Q-I [Fairburn & Beglin, 1994] with instructions [Celio et al., 2004] generates the same overeating data and severity score as the EDE interview. EDE-Q-I will be used across *all assessment points* given its low burden (*in addition to the EDE given during major assessment points*). EDE-Q-I converges well with the EDE as a measure of “change” [Sysko, Walsh & Fairburn, 2005] and has psychometric support in the MBS population [Hrabosky et al., 2008; Grilo et al., 2013].
- **Food Craving Inventory (FCI).** The FCI [White et al., 2002] assesses general and specific food cravings (**relevant for NB**) and comprises four subscales for different food groups. The FCI has been validated and psychometrically supported in studies with obesity and BED [White et al., 2002; White & Grilo, 2005]. Internal consistency was 0.93 for total score and ranged from 0.70-0.85 for subscale items in N=464 patients with obesity at Yale. The use of this craving instrument will allow direct comparison to the leading NB obesity trials [Greenway, Fujioka & Plodkowski, 2010; Wadden et al., 2011] and NIH/NIDDK-funded trials examining NB among patients with BED and obesity.
- **Power of Food Scale (PFS)** *assesses psychological impact of and drive to eat palatable foods*; it measures appetite for, rather than consumption of, palatable foods. PFS has been validated in normative [Lowe et al., 2009] and treatment-seeking obese samples [Cappelleri et al., 2009] and has 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].
- **Patient Health Questionnaire-9 (PHQ-9).** The PHQ-9 is a brief, psychometrically sound, and widely-used measure of depression in diverse medical settings [Kroenke, Spitzer & Williams,

2001]. Post-MBS depression was associated with poorer MBS outcomes in some studies [King et al., 2019; Ivezaj & Grilo, 2015; Yanos et al., 2015] and is relevant to the study medication.

- **Global Physical Activity Questionnaire (GPAQ).** This self-report measure will be used for the assessment of physical activity and sedentary behavior. The NIH ADOPT guidelines of core measures to use in obesity trials [Sutin et al., 2018; MacLean et al., 2018] recommends the use of the GPAQ when actigraphy is not used [Lytle et al., 2018]. Moreover, physical activity is a core treatment target of BWL, and is expected to change with BWL treatment.
- **Medical Outcomes Study Short-Form-12 Health Survey (SF-12).** The SF-36 [Ware & Sherbourne, 1992] is a widely-used 36-item measure of health-related quality of life. SF-36 has well-established reliability and validity [McHorney, Ware & Raczek, 1993; McHorney et al., 1994]. The abbreviated version of the SF-36, the SF-12, is comparable to the SF-36 in patients with and without obesity [Wee, Davis & Hamel, 2008] and also has well-established psychometric validity and reliability and is commonly used in MBS samples [Kolotkin & Andersen, 2017]. The SF generates 2 summary scores (physical & mental quality-of-life). Quality-of-life measures were obtained in the original NB obesity trials [Greenway, Fujioka & Plodkowski, 2010; Smith et al., 2013] and will be relevant to the MBS population.
- **Alcohol Use Disorders Identification Test (AUDIT)** [Babor, de la Fuente, Saunders, & Grant, 1992] is a 10-item measure that assesses alcohol use. The AUDIT has been used extensively and demonstrates high internal consistency and good test-retest reliability (Reinert & Allen, 2007). The AUDIT has also been used among bariatric groups (King, Chen, Mitchell, et al., 2012).
- **Drug Abuse Screening Test-10 (DAST-10)** [Bohn, Babor, & Kranzler, 1991] 10-item measure is a psychometrically sound measure of drug misuse (Yudko, Lozhkina, & Fouts, 2007).

Bloodwork (labs):

- CBC panel will be obtained at baseline to measure anemia for safety. Anemia can occur following bariatric surgery.
- **Lipid profiles** (total cholesterol, HDL-, LDL-cholesterol, triglycerides) will be obtained following established protocols (12-hr overnight fast, no exercise for 48 hr, a.m. draw) [Andersen et al., 1995].
- **Glycemic Control and HbA1c.** Glycemic control will be determined with **HbA1c**, a routine measure of average **glucose** control for a previous (3-month) period. HbA1c, will be drawn at baseline, Stage 1 post-treatment (4 months), Stage 2 post-treatment (7 months) and again at follow-up evaluations, thus ensuring no overlap in the time-periods.
- **Insulin** is a key marker of cardiovascular risk and improved significantly with the combination of NB and behavioral therapy in individuals with obesity [Wadden et al., 2011].
- **Hepatic Function Panel. Liver function** will be assessed throughout treatment for safety reasons.

Treatment Variables:

- **Credibility ratings** will be examined before beginning treatments and again after completing treatments. Placebo/Med Ratings. Patients and clinicians will provide medication versus placebo ratings (i.e., whether they believe active or placebo).
- **Treatment Compliance for BWL** will include session attendance and self-monitoring compliance and counts.
- **Compliance for medication** will include pill count method (determined by blinded clinicians). In addition, we will be able to explore the relationships between compliance (for BWL and for study medications) with the primary outcomes.

- **Adverse Events** will be collected during clinic visits using adverse event checklist of the most commonly reported adverse events for NB and LDX medications. Research-clinicians will ask open-ended and follow-up questions as needed.

5. **Genetic Testing** N/A ☒

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

N=160 participants with regular loss-of-control eating and with obesity (BMI $\geq$ 30 or BMI $\geq$ 27 if with metabolic comorbidity), ages 18-70 years, and meeting other eligibility criteria as described below will be randomized to participate in this trial. Previous work with this population suggests participants will be male and female, and represent diverse racial/ethnic and sociodemographic groups.

7. **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 | |

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

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

Inclusion criteria: To be included in the trial, a prospective participant must:

1. Be in the age range $\geq$ 18 years of age and $\leq$ 70 years of age.
2. Have a BMI $\geq$ 30 (or BMI $\geq$ 27 with a medical comorbidity) and BMI $\leq$ 50
3. Have had laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy
4. Approximately six months post-surgery
5. Experience regular loss-of-control eating (defined as at least once weekly over the past 28 days)
6. Be an otherwise healthy subject without uncontrolled medical problems, as determined by the study physician and medical co-investigators (physical examination, laboratory studies).
7. Read, comprehend, and write English at a sufficient level to complete study-related materials.
8. Provide a signed and dated written informed consent prior to study participation.
9. Be available for participation in the study for up to 19 months (7-month treatment plus 12-month follow up).

Exclusion criteria: To enhance generalizability, exclusion criteria will be minimal, but consistent with study medication prescribing guidelines. A prospective participant will be excluded if he or she:

1. Has a predisposition to seizures (e.g., subject with a history or evidence of seizure disorder, febrile seizures during childhood, brain tumor, cerebrovascular disease, or significant head trauma; has a family history of

idiopathic seizure disorder or is currently being treated with medications or treatment regimens that lower seizure threshold).

2. Has a history of anorexia nervosa or history of bulimia nervosa.
3. Is currently taking a medication that is a contraindication to NB medication (e.g., MAOI, opiates).
4. Is currently using other medications for weight loss.
5. Has a history of allergy or sensitivity to bupropion or naltrexone.
6. Has a co-existing psychiatric condition that requires hospitalization or more intensive treatment (such as bipolar mood disorders, psychotic illnesses, or severe depression)
7. Has untreated hypertension with a seated systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg, or heart rate > 100 beats/minute.
8. Has a history of congenital heart disease, cardiovascular disease, cardiac arrhythmias requiring medication, or a history of cerebrovascular pathology including stroke.
9. Has current uncontrolled hypertension.
10. Has current uncontrolled Type I or Type II diabetes mellitus.
11. Has untreated hypothyroidism with a TSH > 1.5 times the upper limit of normal for the test laboratory with repeat value that also exceeds this limit.
12. Has gallbladder disease.
13. Has a history of severe renal, hepatic, neurological, chronic pulmonary disease, or any other unstable medical disorder.
14. Has a recent history of drug or alcohol dependence (since having bariatric surgery).
15. Is currently in active treatment for eating or weight loss.
16. Is currently participating in another clinical study in which the subject is or will be exposed to an investigational or a non-investigational drug or device.
17. Is breast-feeding or is pregnant or is not using a reliable form of birth control.
18. Reports active suicidal or homicidal ideation.
19. To facilitate enrollment and enhance generalizability for the study's primary aims (Stage 1 RCT and Stage 2 RCT for responders), the following will be additional exclusions only for Stage 2 non-responders because of safety considerations and prescribing guidelines for the LDX medication.
 - a. Age range <18 years of age and >64years
 - b. Previous history of problems with LDX or other stimulants
 - c. Has a history of allergy or sensitivity to LDX or other stimulant medications
 - d. Current medication contraindicated with study medication
 - e. Any current psychostimulant use or any medication for ADHD.
 - f. History or current alcohol or substance use disorder (smoking will not be exclusionary)
 - g. Any history of cardiac diseases.
 - h. LDX is classified as a DEA-controlled substance and product labeling includes a "Warning" that CNS stimulants have high potential for abuse/dependence. Thus, careful evaluation of drug and alcohol problems will occur and a history will be an exclusionary criterion (smoking will not be exclusionary)
 - i. Is currently taking MAOI medication, SSRI medication, or strong inhibitors of CYP2D6 (i.e., Cinacalcet, Fluoxetine, Paroxetine, Quinidine).

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

Participants will be interviewed by a trained research clinician (EDE-BSV) to determine whether they meet criteria for regular loss-of-control eating. These diagnostic clinical interviews (MINI) will also determine whether participants have any co-existing psychiatric conditions (including substance use disorders) that require hospitalization or more intensive/different treatment. The study physician will determine medical

eligibility based on results of participants' physical examination (within one year of starting the study), 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, and a review of systems. Medical review is required for all participants. If the study physician requires additional information, the study physician will contact the treating physician. In addition, the Yale bariatric center will review the Yale participants record for safety and confirm bariatric surgery date and type. Finally, the study physician will review medical records of all participants, including those who did not have bariatric surgery at Yale. Of note, in order to have had recent bariatric surgery (i.e., past six months), comprehensive physical exams would have been conducted for safety.

Source of Research Materials

Data will be collected in the form of standardized clinical interviews, self-report questionnaires, clinical interviews, and traditional medical methodologies including standard laboratory blood tests. All the assessments are described in the previous section (Research Design). The data will be used for clinical and research purposes only.

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

The primary risks of this study are the behavioral weight loss therapy (BWL), the pharmacologic therapy with LDX, the pharmacotherapy with NB, placebo during Stage 1 and 2 RCT, the assessment procedures, and lack of efficacy.

- 1) **BWL:** Behavioral weight loss (BWL) is an established and widely-used intervention for BED (which involves regular loss-of-control eating) and obesity. The only foreseeable risks include some mild discomfort or embarrassment when discussing eating patterns or body image concerns. 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. Thus, the risks of BWL are judged to be minimal.
- 2) **NB:** Naltrexone/Bupropion combination (NB) is FDA approved for the treatment of obesity. NB has demonstrated safety, tolerability, and efficacy for patients with obesity treated over much longer periods of time (>12 months) than in the present study (Greenway et al., 2010). 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. Less common side effects include risk of seizure, increase in blood pressure and heart rate, hepatotoxicity, and angle-closure glaucoma. 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 Naltrexone/Bupropion and placebo (1.6% versus 1.4%) and none of the observed events were judged to be related to the study. Since one of the study's medication may be a combination Naltrexone/Bupropion, in keeping with the FDA advisory pertaining to antidepressants, including bupropion, the following information will be included in the study consent forms:

"The U.S. Food and Drug Administration (FDA) has issued an Advisory cautioning health care providers, patients, and families to closely watch individuals taking bupropion for signs of their depression getting worse and for thoughts of killing or harming themselves, especially during the first several weeks that bupropion 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)."

- 3) **LDX:** Lisdexamfetamine (LDX) is the only FDA-approved medication for the treatment of BED. LDX has demonstrated short-term effectiveness relative to placebo and safety in one phase 2 and two phase 3 RCTs. An additional Phase 3 open-label 12-month extension safety and tolerability trial of LDX for BED with N=604 patients who completed previous Shire RCTs (McElroy et al., 2015, 2016) reported the 12-month safety/tolerability profile of LDX was consistent with short-term (12-week) BED trials and with established profile of LDX for ADHD (FDA-approved); 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation (Gasior et al., 2017).

LDX was associated with the following side effects 10% or more of the time and twice as often as placebo: dry mouth and insomnia. LDX was associated with the following side effects in less than 10%, but twice as often as placebo: decreased appetite, increased heart rate, feeling jittery, constipation, anxiety, diarrhea, decreased weight, hyperhidrosis, vomiting, gastroenteritis, paresthesia, pruritis, upper abdominal pain, energy increased, urinary tract infection, nightmare, restlessness, and oropharyngeal pain.

Serious risks of LDX include psychiatric problems and heart complications, including sudden death in people who have heart problems or heart defects, and stroke and heart attack in adults. Central nervous system stimulants, including lisdexamfetamine, may cause psychotic or manic symptoms, such as hallucinations, delusional thinking, or mania, even in individuals without a history of psychotic illness.

LDX is associated with increased risk of serotonin syndrome when co-administered with serotonergic agents, but also during overdose situations. The potential for a pharmacokinetic interaction exists with co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to the active metabolite dextroamphetamine.

This study will provide LDX following the same dosing and procedures and time frame (12-weeks) as the large phase 2 study demonstrating safety and optimal dosing and two large phase 3 trials reporting safety and efficacy for BED over 12-week treatments. The same optimal dosing strategy will be used in the Stage 2 maintenance RCT; this delivery safety is further supported by the Hudson et al (2017) report of LDX vs placebo maintenance. LDX is also classified as a DEA-controlled substance and product labeling includes a "Warning" that CNS stimulants have high potential for abuse/dependence.

- 4) **Placebo:** Placebo, which is a risk only during the Stage 2 treatment, is considered a generally inert comparison condition and participants may not improve or sustain improvements with the passage of second 12-week treatment stage. Such placebo controls have been utilized in numerous published trials with BED without problems and RCTs have reported that some persons do improve solely on placebo.
- 5) **Assessments:** Completion of the assessment procedures may cause some mild anxiety or embarrassment to some patients. Drawing blood from a vein to perform necessary laboratory tests is quite safe. Sometimes a bruise will occur at the puncture site and on very rare occasions a blood clot or infection may occur. If this occurs, appropriate treatment will be instituted immediately.
- 6) **Failure to Improve:** There is a chance that the patient's LOC eating may fail to improve or may worsen during the study. Patients will be withdrawn from the study if their clinical condition deteriorates to a

significant degree. Our experience with numerous RCTs is that this is quite rare. In the case of non-responders to Stage 1 treatments, if warranted due to clinical status and/or if participants request, appropriate referrals will be provided.

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

BWL and Interviews: The research clinicians in this study and additional research staff will be carefully trained and supervised by the Investigators in their procedures, assessments, and evaluations. The clinical evaluators are carefully trained and supervised research clinicians (doctoral level and/or advanced trainees). All of these clinical-research staff who have multiple contacts with the participants can reasonably be expected to identify potential problems. They are expected given their experience and training to identify any problems or distress and to take appropriate action as medically indicated. The study investigators will be continuously available to the research clinicians and to the independent evaluators to discuss any problems and to implement any needed interventions or offer appropriate referrals. The repeated detailed assessments during the course of treatment (and the two follow-up assessments) will allow for additional and ample opportunity to identify difficulties. In the event that a participant experiences undue distress, ample resources at Yale are available.

NB: The NB pharmacologic treatment protocol follows the evidence-based dosing that has demonstrated safety, tolerability, and efficacy for obesity treated over much longer periods of time (>12 months) than the present study. 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 Naltrexone/Bupropion and placebo (1.6% versus 1.4%) and none of the observed events were judged to be related to the study. 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 as well as the verbal consent process: *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.* In addition to structured MINI and clinical diagnostic interviewing and medical record reviews, we will perform lab test with potential subjects suspected of opiate usage.

Monitoring of Depressive Symptoms. In response to the FDA advisory, depressive symptoms will be monitored frequently. To monitor changes in depressive symptoms, patients will be asked to complete the PHQ-9 at monthly clinic visits. The research clinicians, who are trained and supervised by licensed psychologists in suicidal assessment, will review PHQ-9s during the clinic visit, and will ask pointed questions pertaining to suicidality/suicidal ideation (i.e., suicidal thoughts, plan, means, and intent) using the Columbia Suicide Severity Rating Scale. If it appears, based on the clinical judgment of the research clinician, that the participant is experiencing significant adverse effects of the medication, the investigators and study physician will be consulted and a determination of whether to discontinue the medication will be made. The participant will be asked to continue to follow-up assessments (if applicable). If warranted, the participant will be given a referral and safety planning will be implemented. If any participant experiences adverse reactions, or if side effects are too severe, the medication will be discontinued.

Finally, risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding co-administration with high-fat meal. Increase in Blood Pressure and Heart Rate: Monitor blood pressure and heart rate in all patients. 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.

Participants must agree to inform their primary provider (or treating surgeon if they are under his/her care) that they are enrolling in a clinical trial that involves taking a study medication (combination Naltrexone+Bupropion for Stage 1; combination Naltrexone+Bupropion for Stage 2 responders or Lisdexamfetamine for Stage 2 non-responders).

LDX: Effective screening will exclude all prospective participants who would be at greater risk for complications because of medical or psychiatric illnesses. LDX is classified as a DEA-controlled substance and product labeling includes a “Warning” that CNS stimulants have high potential for abuse/dependence. Thus, potential participants with a history of drug and alcohol problems will be excluded and all participants in the RCT will be evaluated carefully at all clinic visits for any signs of medication misuse in addition to structured assessments of potential side-effect or adverse events per the published procedures (McElroy et al., 2015). In addition, the “warning” will be included in the informed consent form and process. The LDX pharmacologic treatment protocol follows the evidence-based dose-optimization protocol that has demonstrated safety, tolerability, and efficacy during the 12-week duration of treatment. Subjects will be evaluated repeatedly throughout the study and will be monitored for any signs of medication misuse and for side-effects and adverse reactions using structured assessments at all clinic visits. If any participant experiences adverse reactions, or if side effects are too severe, the medication will be discontinued. Regarding the risk of serotonin syndrome, all SSRI medication and strong inhibitors of CYP2D6 will be excluded for this non-responder arm of the study. Regarding risk of heart complications, individuals with a history of cardiac disease will be excluded. Regarding psychiatric symptoms, such as mania and psychosis: At monthly follow-ups during Stage 2, study clinicians will assess manic and psychotic symptoms using structured questions from the Mini International Neuropsychiatric Interview (MINI), a well-established interview used to assess psychiatric disorders. This added specific assessment will be conducted with participants aged 30 years or less (given previous LDX trial report that 0.1% of those patients might have developed such symptoms). Any older patients assessed who are suspected of having such symptoms would also be assessed carefully. We note that subjects with history of psychotic or bipolar illness are excluded from participating and this should minimize such risks. Study clinicians are supervised by licensed psychologists trained and experienced in psychiatric assessment. If participants endorse manic or psychotic symptoms (or any of the other potential symptoms of concern), clinicians will consult with the study investigators for safety management and treatment planning. **Monitoring of depressive symptoms is described above.**

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. 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.

Medication Titration & Taper.

NB: NB titration is described on page 10 of the protocol. Participants on placebo will take the same number of pills as the active group to maintain the blind. Participants will be cautioned against stopping the NB abruptly. For NB, taper off is not medically necessary for participants on the study medication for 4 weeks or less.

Non-responders LDX: Participants will have up to three weeks of up-titration: one pill daily (30 mg/day; 1 week), then one pill daily (50 mg/day; 1 week), then one pill daily (70 mg; 1 week) based on acceptable tolerability and clinical need). If 70 mg is not tolerated, downward titration to 50 mg/day can occur. For the remaining treatment (weeks 4-12), the optimized LDX dose (50 or 70 mg/day) will be maintained. LDX down-titration: 70 mg to 50 mg for 2 days, then 30 mg for 2 days, to discontinue medications. At the end of Stage 2, participants on placebo will take the same number of pills as the active group to maintain the blind.

Assessments: We will 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). Blood pressure and heart rate will be measured during all evaluation visits. Two readings will be taken at each assessment. In the event of systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, or an increase in heart rate of ≥ 15 bpm (from baseline), the study physician will be notified and will determine whether additional intervention and/or medication discontinuation is warranted. Liver function. Participants with severe hepatic disease will be excluded if this is detected at baseline, per exclusion criteria. Liver function will also be repeated in the Stage 2 RCT for responders who are re-randomized to NB or placebo at month-1 clinic visits. The study physician will review results of a hepatic panel prior to the start of treatment and throughout treatment. Any changes and out-of-range values will be flagged immediately by research clinicians, and the study physician will determine whether additional intervention and/or medication discontinuation is warranted.

Given the uncertain effects of medication during pregnancy, the following precautions will be taken for women of reproductive age who are sexually active: 1) a pregnancy test will be required at Stage 1 and Stage 2 (but only for those who will be re-randomized to treatment in Stage 2), 2) will be required 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, and 3) if a woman becomes pregnant after study entry, her medication will be discontinued. A pregnancy test will be given to all female participants of reproductive age, regardless of initial randomization assignment.

Failure to Improve: There is a chance that the patient's loss-of-control eating may fail to improve or may worsen during the study or that patients will not lose weight. Patients will be withdrawn from the study if their clinical condition deteriorates to a significant degree. Our experience with numerous RCTs is that this is quite rare. In the case of non-responders to Stage 1 treatments, Stage 2 RCT will test another pharmacologic treatment strategy. If warranted due to clinical status and/or if participants request, appropriate referrals will be provided.

Protecting Confidentiality: To ensure confidentiality, all participant research records will be kept in locked files in the Department of Psychiatry at the Yale University School of Medicine. All research forms, interviews, measures, audiotapes, and computer data will be coded to ensure anonymity and will be kept in separate locked files. Data analysis and reporting will not allow for identification of any individual participants. All research personnel will be trained and supervised around confidentiality issues. The training will include formal NIH or Yale IRB modules with testing certification as well as HIPAA guidelines to follow around confidentiality. 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. 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 Human Investigation Committee (HIC), may have access to the research records. Additionally, the funding agency (NIH) may have access to the research records. The subject'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 HIC and HIPAA procedures.

Informed Consent: Research clinicians (who have completed IRB and ethics training) will meet with potential participants to discuss the study and all procedures, treatments, and risks and obtain written informed consent. All potential participants will be free to decide whether or not to participate and are free to

withdraw from the study at any time. Alternative treatments (both psychosocial and pharmacological options) will be discussed and referrals offered if requested. The written informed consent will be obtained after opportunity to discuss and address all questions. 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. A decision to not participate or to discontinue participation would not adversely influence future interactions with Yale, Yale School of Medicine, or the investigative group. The process of informed consent may be completed in-person or remotely. If completed remotely, the consent process will be conducted by one of two methods: 1) a consent form will be mailed or emailed to the participant. The participant will then mail back (or email back) the signed consent form to the study team for signature or 2) the consent form will be completed using the validated Part 11 version of REDCap. A copy of the final consent (signed by both parties) will be mailed or emailed to the participant for his/her records. For all consenting, a meeting will be held in-person or remotely (e.g., via Zoom) to discuss the study and informed consent process.

12. 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.)

- a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

Greater than minimal risk

Although this study qualifies as clinical trial research, it does not meet NIH criteria for Phase III clinical trial research. Nonetheless, this study will be monitored twice yearly by a Data Safety Monitoring Board (DSMB) as the study involves double-blind placebo controlled evaluation of medication effects that may involve greater than minimal risk. Adequate surveillance and protections will be put in place to discover adverse events promptly and keep their effects to a minimum. The treatment interventions and assessment protocols are well-established and pose primarily low risks to subjects. The DSMP focuses on close monitoring by the PI (Grilo) in conjunction with the study MD (Dr. Jastreboff). Excessive adverse events and/or any serious events (should they occur) will be reported promptly to the NIH and to the IRB (Human Investigation Committee) at the Yale University School of Medicine. In addition to the DSMP, the Yale IRB reviews all aspects of the study protocol (including progress and problems) minimally once per year.

- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? NA
- c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here <http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates> for
- i. Minimal risk
 - ii. Greater than minimal

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews semi-annually. Although this study qualifies as clinical trial research, it does not meet NIH criteria for Phase III clinical trial research. Nonetheless, this study will be monitored semi-annually by a Data Safety Monitoring Board (DSMB) as the study involves a double-blind placebo controlled evaluation of medication effects that may involve greater than minimal risk. Adequate surveillance and protections will be put in place to discover adverse events promptly and keep their effects to a minimum. During the review process, the principal investigator and DSMB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

Either the principal investigator, the IRB or the DSMB have the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed greater than minimal. Although we do not view the risks associated with the study medication as minimal risk, the established safety and validity of the LDX (FDA-approval of Vyvanse for BED) and Naltrexone/Bupropion (FDA-approval of Contrave for obesity) medications in RCTs suggest that the study procedures and medications are not high risk.

Although we have assessed the proposed study as one of greater than minimal 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. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

DATA AND SAFETY MONITORING PLAN

Monitoring for data integrity and safety will be the responsibility of the investigators and the Yale IRB (Human Investigation Committee). The data safety monitoring plan (**DSMP**) for this clinical trial focuses on close monitoring by the principal investigator and study physician in conjunction with the safety officer (**SO**): this allows monitoring of reported participant level event data in real time. The SO will document agreement or disagreement with the principal investigator and whether any action is required. In addition to this real-time monitoring, the **DSMB** will perform study oversight and monitoring including data quality, storage, confidentiality, and issues covered in good clinical practice. In addition, the principal investigator will promptly report excessive adverse events and any serious adverse events to the NIH and to the IRB at the Yale University School of Medicine. Other (less serious) adverse events will be reported to the IRB periodically during regular quarterly reporting periods.

A Data and Safety Monitoring Board (DSMB) will monitor this project. This board is already in place at Yale and has successfully monitored the PI's current trials with the proposed study medications. The DSMB is composed of Yale investigators who are independent of the proposed trial and experienced in various aspects relevant to the current proposal including: conduct of clinical trials, biostatistics, and the clinical management of obesity, eating/weight disorders, and psychiatric/behavioral health.

We have developed a standard DSMB report form that summarizes, *on a twice-yearly basis*:

1. Recruitment, retention, and follow-up rates for the study and compares them to target rates.
2. Rates of data completeness and availability of primary outcome data
3. Occurrence of AEs and SAEs
4. Report of study progress since the last report.
5. Rates of recruitment of women and minorities with respect to targets.

These reports are generated by the study coordinator each quarter (reviewed by PI and Study Physician) and – on a twice-yearly basis – will be again be re-reviewed by PI and submitted to the DSMB. DSMB comments are documented and forwarded to the Yale IRB at the time of the annual review and re-approval. They will also be summarized as part of the annual progress report to NIDDK. However, if adverse events occur in greater magnitude or frequency than expected these will be reported to the DSMB, HIC, and NIH prior to scheduled reports. The Principal Investigator will assume full responsibility for reporting serious and non-serious and unanticipated adverse events. The DSMB may call an ad-hoc meeting to address emergent safety concerns.

Because the projected effect sizes may not be large enough for detection during interim analyses, we are not proposing a preliminary analysis of accumulating efficacy and safety data by treatment assignment. Instead, we propose to submit a twice-yearly report of aggregate data to the DSMB members that contains screening data, baseline demographics, retention data, serious adverse events data, as well as accrual status, and any other data that will help in the assessment of the clinical trial. Based on this report, each DSMB member will complete a form making one of two recommendations: 1) continue recruitment as planned; or 2) schedule formal DSMB meeting immediately. If any DSMB member recommends a meeting, this will be scheduled, minutes will be kept, the report will be reviewed with the PI, and the committee will vote on whether the study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop recruiting pending further investigation; and 4) the Yale IRB will be informed.

Risk Assessment:

The risks associated with the current study are deemed greater than minimal. Although we do not view the risks associated with the study medication as minimal risk, the established safety and validity of the Naltrexone/Bupropion (FDA-approval of Contrave for obesity) and LDX (FDA-approval of Vyvanse for BED) and medications in RCTs suggest that the study procedures and medications are not high risk.

Although we have assessed the proposed study as one of greater than minimal 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. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Measurement and reporting of adverse events.

Adverse event data will be collected on an on-going basis. These data will be collected and examined with blindness to the medication conditions. Adverse events data will be reviewed by the PI, co-investigators, and the safety officer (SO) throughout this trial (see Table below). A summary of adverse events will be provided to the Yale IRB yearly during the annual renewal review process. Any serious or unanticipated adverse events will be reported to the NIH and to the Yale IRB within 48 hours.

The frequency of data review is summarized in the following table:

Table	Data type	Frequency of Review by PIs and Research Team	Frequency of Review by PI and DSMB
Table 1	Subject accrual	Monthly	Twice Yearly
Table 2	Treatment completion rates (retention/attrition)	Quarterly	Twice Yearly
Table 3	Adverse and serious adverse event rates	Quarterly	Twice Yearly
Table 4	Checklist for DSMB	NA	Twice Yearly

Attribution of Adverse Events:

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

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

Plan for Grading Adverse Events:

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 adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
- 4. Severe adverse event that may jeopardize the participant's health and requires medical or surgical intervention to prevent death, disability/incapacity, or congenital anomaly.
- 5. Fatal adverse event

Plan for events to the Yale IRB that are unexpected AND related AND involve risk of harm to subjects or others:

The PIs will report any incident, experience, or outcome that meets all three of these conditions to the IRB immediately: a) unexpected (in nature, specificity, severity, or frequency); b) related (probably or definitely); and c) places participants or others at greater risk of harm (physical, psychological, economic, legal, or social) than previously known or recognized. Following immediate reporting, an event will be reported using Form 710 FR 4 (Unanticipated Problem Involving Risks to Subjects or Others Reporting Form) to the IRB within 5 calendar days of it becoming known to the PI.

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitors, e.g., study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies:

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

- i. All Co-Investigators listed on the protocol
- ii. National Institutes of Health

The investigators will conduct a review of all adverse events upon completion of every study subject. The investigators will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Procedures for providing follow up care:

Medical monitoring will occur at all clinic and follow up visits and medical care will be provided if warranted. If a study participant experiences any psychiatric symptoms or distress (e.g., depressive symptoms or suicidality) at any stage of study participation he/she will receive short-term treatment and support from the study treatment team (including psychologists) and will be connected to a local emergency department (e.g., the Crisis Intervention Unit at Yale-New Haven Hospital) and his/her physician or therapist for ongoing care.

Measurement and reporting of subject accrual, adherence to inclusion/exclusion criteria.

Review of the rate of subject accrual and adherence to inclusion/exclusion criteria will occur regularly by the PI and co-Investigators and yearly by the safety officer. These reviews will help to assure that participants meet eligibility criteria and ethnic diversity goals outlined in the grant proposal.

Measurement and reporting of participant treatment completion rates.

Participation rates (retention and attrition) will be reviewed on an ongoing basis by the PIs and co-investigators to identify any potential problems, and formally by the PIs and DSMB twice-yearly. Any differential dropout across blinded study groups and/or higher than expected dropout will be reviewed by the investigators to determine whether any problems are present and what, if any, corrective action needs to be taken.

During the reviews, if the DSMB has concerns about whether attrition has reached a level that might inhibit the ability of the study to address its primary aims, they will suggest a meeting to discuss methods for improving subject retention. Previous pharmacotherapy studies for BED (with comparable time frames for pharmacotherapy) have reported attrition rates between 20% and 38%. Studies of NB for obesity treatment reported attrition of 30% to 45%. Thus, “trigger points” for review and discussion by principal investigator and research staff will be: 35% (“low alert”), 40% (“mid alert”), 45% (“high alert”), 50% (“extreme alert”). With early alerts to problems, action would be taken to avoid higher level alerts; if a higher level alert should arise, more drastic actions would be taken.

Trial Stopping Rules

Given that this study is deemed greater than minimal risk to human subjects, it is more likely that attrition or difficulty in recruiting adequate numbers of participants will require stopping the trial than would excess adverse events. However, as outlined, adverse events will be monitored in all participants, and the safety officer, together with the PI, will alert the Yale IRB and the NIH if a larger (or more serious) than reasonably expected adverse event rate should occur. Other potential issues relating to stopping rules for this trial include:

1. New Information

It is unlikely that any new information will become available during this trial that would necessitate stopping the trial. If new safety data (i.e., pertaining to short-term use of the study medication) become available, this will be evaluated.

2. Limits of Assumptions

It is possible that baseline differences between the treatment conditions, excessive attrition, and/or missing data could limit the value of data analysis. Baseline differences across blinded treatment groups, if present, will be evaluated yearly and considered in relation to potential effects on the power to detect differences in the primary outcomes. If these effects were to develop and be sizeable, alterations to the randomization schedule would be considered. Any plans to alter the randomization scheme would be communicated to the NIH.

The following actions would be taken at each level of alert:

(1) Low-level alert = Review of potential problems by PI.

(2) Mid-level alert = Meeting with co-investigators to discuss approaches to minimize further losses to follow-up/dropouts.

(3) High-level alert = Meeting with co-investigators to determine further alterations of study protocol to complete the study with no further losses.

(4) Extreme-level alert = In the unlikely event of a 50% dropout rate prior to the mid-study time point, discontinuing the trial would be considered.

3. Limits of Rules

There are other situations that could occur that might warrant stopping the trial and/or including a section on the safety report entitled “Other situations that have occurred since the last safety report that warrant discussion” to allow for communication of concerns.

Finally, as currently outlined above, the DSMB has the authority to stop the trial following any serious adverse event or following reviews of adverse events.

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

DATA ANALYSIS

Baseline demographic and clinical characteristics for the randomized groups will be compared using chi-square tests for categorical variables, and 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. Dropouts and completers will 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.

Overall analysis strategy: *Mixed-effects models* (Diggle et al, 2002, Gueorguieva & Krystal, 2004) will be used to compare treatments. These models allow for different numbers of observations per subject, use all available data on each subject, 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, 1997; 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, treatments, and all possible interactions, and random subject-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 post-MBS patients with LOC for (a) reducing LOC eating and (b) reducing weight.* In the mixed models, the dependent variables will be (a) reduction in LOC eating frequency, and (b) percent change in weight (%TWL).

Significant BWL and NB main effects will be considered supportive of our primary aim 1 hypotheses. *We anticipate NB will be associated with significantly greater reductions in LOC eating and weight than placebo, and that BWL will be associated with significantly greater reductions in LOC eating and weight than no-BWL.* The factorial design will also be able to assess for interactive (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) *Examine effectiveness* of BWL and NB medication, alone and in combination, on secondary outcomes: remission (zero LOC-eating past 28 days); behavioral/psychosocial functioning (eating-disorder psychopathology (EDE-BSV), food craving (FCI) and reward (PFS), depression (PHQ-9), physical activity (GPAQ), and quality-of-life (SF-12)); and cardiometabolic risk factors (change in lipids, HbA1c, glucose, insulin, and neck circumference). To compare remission rates across groups we will use logistic regression with BWL, NB and the interaction as fixed effects. Significant main effects of BWL and NB will be considered supportive of our hypothesis. We will also test the interaction of the two treatments. Continuous secondary outcomes will be analyzed using the same approach as for primary aim 1. However, due to multiple secondary outcome variables, we will interpret as significant effects those with p-values smaller than the Bonferroni-adjusted cutoff of 0.01 rather than the 0.05 significance level used for the primary aim. *We anticipate NB will be associated with significantly greater reductions in behavioral/psychosocial symptoms and cardiometabolic risk factors than placebo, and that BWL will be associated with significantly greater increases in physical activity (GPAQ) in addition to reductions in behavioral/psychosocial symptoms and cardiovascular risk factors than no-BWL. We do not have a priori hypothesis regarding the interaction but will test it together with the main effects.*

(B) *Explore conceptually- and empirically-supported predictors, moderators, and mediators* of primary outcomes (LOC eating and weight changes). In terms of treatment processes, we will attempt to replicate our findings regarding the prognostic significance of rapid response for behavioral and pharmacologic treatments (Grilo et al., 2006, 2012, 2015; Masheb & Grilo, 2008). We will follow Kraemer's (2002) conceptual/statistical models for exploring *predictors, moderators and mediators* for both LOC eating and weight change outcomes. Per Grilo et al. (2012), we expect depression (PHQ-9) levels and overvaluation of shape/weight (EDE-BSV), which is also characteristic in MBS with LOC patients (Ivezaj, Wiedemann, & Grilo, 2019), to be significant predictors and moderators. These results would inform future treatment prescription regarding behavioral and pharmacologic interventions for post-MBS. 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 (EDE-Q) and physical activity (GPAQ) constructs *relevant to BWL*, food-craving/reward constructs (FCI, PFS) *relevant to putative mechanisms of action for NB*, and depression (PHQ-9) a conceptual/empirically-supported construct, *will yield relevant change variables for analyses of mediation* (i.e. testing *subsequent* changes in LOC eating and weight).

STAGE 2 RCT – SECONDARY AIM: *Among responders to Stage 1 treatments*, to **test** effectiveness of NB medication relative to placebo for enhancing maintenance and longer-term outcomes. Primary outcomes will be (a) **"relapse"** to DSM-5 (and ICD-11) level of once-weekly LOC eating and (b) **weight regain**. Secondary outcomes *will be LOC eating frequency, weight changes, eating-disorder pathology, and depression.* *For the primary outcome (predicting relapse)*, we will follow analytic strategy of studies testing medication for maintenance (i.e., LDX) for BED (Hudson et al., 2017) and (i.e., fluoxetine) for bulimia nervosa (Romano et al (2002). Stage 2 NB and placebo will be compared on the proportion of Stage 1 responders who "relapse" using chi-squared tests and Cox Proportion Hazards Tests; we will explore further using survival analyses to estimate whether time to relapse differs between NB and placebo. *For the secondary outcomes*, we will use mixed effects models to assess whether significant differences in changes occur between the NB and placebo groups.

We anticipate that subjects randomized to NB maintenance will maintain better outcomes than patients randomized to placebo.

Finally, we will perform an *exploratory analysis of whether Stage 1 treatment is a moderator of medication effects during Stage 2*. To explore this, we will include treatment during phase 1 (BWL, NB) and its interaction with medication in models above. We will estimate effect sizes for outcomes.

STAGE 2 RCT – EXPLORATORY AIM: Alternative Medication (LDX vs Placebo) for Non-responders: *Among Non-responders to Stage 1 treatments, we will explore whether a new medication (an alternate medication with distinct mechanisms of action) enhances outcomes. We will compare LDX versus placebo for reducing LOC eating and will examine weight changes. We anticipate that mixed models will reveal greater reductions in LOC eating and weight with LDX than placebo.*

POWER ANALYSIS

Study sample size was calculated *have at least 80% power (at 2-tailed alpha level 0.05) to detect clinically meaningful effects in Stage 1 RCT for primary outcomes (LOC eating and weight change) and Stage 2 RCT for primary outcome (relapse) at 2-tailed level of 0.05 based on documented effects of the treatments (BWL and NB)*. Below are the specific power calculations.

Stage 1 RCT: *Reported effect sizes for naltrexone/bupropion effects on **dimensional weight loss** are large (d=0.76 in Apovian et al (2013), d=0.98 in Greenway et al. (2010), 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 powered our primary Stage 1 RCT study to detect medium effect sizes. With 40 subjects in each cell of the design, we will 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 the Dr. Grilo's recent RCT with post-MBS patients with LOC eating and RCTs with similar patient groups with obesity with co-existing BED (87% in Grilo, Masheb, & Salant, 2005; 84% in Grilo, White et al., 2013; Grilo et al., 2020).*

For analyses of **remission from LOC eating**, we note remission rates from binge-eating for BWL for BED from our previous RCTs were 50% (Grilo & White, 2013) and 74% (Grilo et al., 2020; see Preliminary Research above); 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 were estimated at 10-15% (based on McElroy (2015)) placebo rates for BED 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.

For analyses of the **dimensional secondary outcome measures**, we are powered to detect medium effects (d=0.6, f=0.3) with 80% power at two-sided adjusted alpha level of 0.01 accounting for 20% dropout. Such effect sizes are clinically meaningful and in line with medium size effects reported by Wadden et al (2011) for cardiovascular risk factor variables and psychosocial quality-of-life measures.

Stage 2 RCT (Test of NB versus Placebo for Maintenance): *Based on our previous RCTs for binge eating and specifically for LOC eating post-MBS, we anticipate 70-75% of subjects on BWL and/or NB will be responders.*

This yields a sample size of 94 to 100 (i.e., 84-90 from active treatments plus 10 from placebo) for randomization to Stage 2 NB or placebo. Thus, if we base power calculation for Stage 2 RCT (testing NB versus placebo for maintenance) on 94 subjects (47 per group) and account for 20% dropout, *we have at least 80% power to detect a medium to large effect size* ($d=0.65$) for the difference between NB vs placebo at 2-tailed alpha of 0.05. For relapse, we can detect *at least* 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 Test of Alternative Medication (LDX) for Non-responders): With N=60 *non-responders* (30 per group with NB or placebo, we would have 80% power to detect $d=0.70$ (remission rates of roughly 5% vs 35%, 15% vs 50%, 30% vs 67%) at 2-tailed alpha level of 0.05 assuming up to 20% dropout.

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

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

A. RADIOTRACERS ☒ N/A

B. DRUGS/BIOLOGICS ☐ N/A

1. If an **exemption from IND filing requirements** is sought for a clinical investigation of a drug product that is lawfully marketed in the United States, 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:	
1. 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.	☒
2. 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.	☒
3. 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	☒
2. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

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

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

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

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

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

Exempt Category 3

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

Exempt Category 4

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

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

NALTREXONE/BUPROPION (Stage II Medication for Non-Responders)

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 the generics naltrexone (50 mg/day) combined with bupropion (300 mg/day) taken daily; matching frequency for placebo).

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 [Marsh et al., 1999]. Naltrexone produces weight loss in lab animals but only minimal weight losses in people [Lavori & Dawson, 2007; Almirall et al., 2014]. Bupropion operates through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms [Smith et al., 2019]. Bupropion may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and reduced weight gain during smoking cessation [Kalarchian et al., 2013; Krippl et al., 2018]. Bupropion promotes weight loss [56]: 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 [Almirall et al., 2012] 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 [Almirall et al., 2014]. The anorectic effects of leptin result from its excitatory effects on pro-opiomelanocortin (POMC) neurons in the hypothalamus melanocortin system [Chen et al., 2017; McElroy et al., 2015]. Stimulated POMC signaling decreases food intake, increases energy expenditure, but is then inhibited by endogenous feedback [Chen et al., 2017]. Thus, combining these two drugs will stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) [Rusch & Andris, 2007; Almirall et al., 2014]. This synergistic model received support both in vitro and in vivo studies [Rusch & Andris, 2007; McElroy et al., 2016].

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 [Rusch & Andris, 2007; Elder et al., 2018; Mond et al., 2010; Citrome, 2015]. 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 pills. Most recently, Apovian, Aronne [Goldschmidt, 2017], 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% [Elder et al., 2008]; 52% vs. 15% [Gasior et al., 2017]. Thus, the proposed RCT study will test the effectiveness of Naltrexone/Bupropion relative to placebo for reducing LOC-eating and producing weight loss in adults with LOC eating and obesity following MBS.

Risks. Several large-scale studies have found that this medication is safe and effective for the treatment of obesity [Rusch & Andris, 2007; Elder et al., 2008; Mond et al., 2010; Citrome, 2015]. 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 co-administration 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 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.

LISDEXAMFETAMINE DIMESYLATE

An important recent development was the FDA approval in January 2015 of a CNS stimulant, lisdexamfetamine dimesylate (LDX), for the treatment of moderate-to-severe BED based on findings from an integrated series of studies funded by Shire (the manufacturer). The phase II (11-week) RCT demonstrated dosing response and that 50mg and 70mg were superior to placebo (McElroy et al., 2015). Two identically designed phase III RCTs testing LDX (50–70 mg dose optimization) for moderate-to-severe BED in adults (McElroy et al., 2016) found LDX superior to placebo 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 11 weeks of treatment. Primary analyses of reduction in binge-eating frequency significantly favored LDX placebo in both phase-III RCTs, with effect-size of 0.83 and 0.97 (McElroy et al., 2016). Another much smaller

RCT with N=50, also funded by Shire, reported weaker advantage of LDX over placebo (ES = 0.50), suggesting the need for further and continued investigation by other researchers. McElroy et al (2017) reported time-course data for binge-eating and associated outcomes to expand upon the McElroy et al (2015) report regarding the significant reductions (over 80%) in binge-eating with LDX; these analyses suggest an early and rapid response (and are supportive of our proposed definition of “response”. The efficacy and safety data were reviewed and appear to represent a favorable benefit-to-risk ratio (Citrome, 2015).

LDX was also associated with significant acute weight loss relative to placebo (mean 4.9 kg) (McElroy et al., 2015, 2016); weight loss was examined as a safety measure. The FDA-approval and manufacturer product labeling include a “Limitation of Use” highlighting that LDX is not indicated for weight loss (because other CNS stimulant medications for weight loss have been associated with cardiovascular problems and the safety and efficacy of LDX for obesity remains uncertain). In the present study, we anticipate that LDX will produce short-term weight loss and the key and novel research goals will involve the questions of the utility of LDX post-MBS.

More recently, two Shire-funded studies have been reported, both providing further support for the proposed research. A Phase III open-label 12-month extension safety and tolerability trial of LDX for BED with N=604 patients who completed previous Shire RCTs (McElroy et al., 2015, 2016) was completed (Gasior et al., 2017). Gasior et al (2017) reported the safety/tolerability profile with 12-months of LDX was consistent with short-term (12-week) BED trials and with established profile of LDX for ADHD (FDA-approved); 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation. Hudson et al (2015 ACNP conference), in a double-blind RCT, reported LDX was significantly superior to placebo for preventing relapse following clinical response to open-label LDX (3.7% vs 32.1% relapsed, respectively). These findings suggest short-term treatment extension with LDX may be effective for decreasing relapse amongst initial responders to LDX. Importantly, Hudson et al (2015) did not report follow-up data after discontinuing the maintenance treatment and whether LDX enhances maintenance for responders to other treatments is unknown.

Putative mechanisms of action for LDX. LDX (l-lysine-dextroamphetamine), is a prodrug of d-amphetamine covalently linked to l-lysine, that when metabolized to d-amphetamine (active form) is a moderately potent inhibitor of DAT, NET, and VMAT2, with little affinity for SERT; its net effect is increased catecholamine availability (Guerdjikova et al., 2016; Hutson et al., 2014; Pennic, 2010; Comiran et al., 2016). LDX seems relevant for reducing binge-eating per preclinical and clinical (Vickers et al., 2015; Wang et al., 2011), and neurobiologic (fMRI) findings suggestive that binge-eating is related to dysfunctions in the dopamine and norepinephrine systems (Balodis, Grilo, & Potenza, 2015; Balodis, Grilo et al., 2013), which play important roles in regulating eating behaviors and reward (Wellman, 2005; Palmiter, 2007).

Risks. LDX is classified as a DEA-controlled substance and product labeling includes a “Warning” that CNS stimulants have high potential for abuse/dependence. Thus, as previously mentioned, potential participants with a history of drug and alcohol problems will be excluded and all participants in the RCT will be evaluated carefully at all clinic visits for any signs of medication misuse in addition to structured assessments of potential side-effect or adverse events per the published procedures (McElroy et al., 2015). Research has found that 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation (Gasior et al., 2017). In addition, the following side effects were reported in adults with BED taking LDX and at least twice as often as the placebo: dry mouth (36%), insomnia (20%), decreased appetite (8%), increased heart rate (7%), feeling jittery (6%), constipation (6%), anxiety (5%), diarrhea (4%), decreased weight (4%), hyperhidrosis (4%), and the following side effects occurred at 2% (vomiting, gastroenteritis, paresthesia, pruritis, upper abdominal pain, energy increased, urinary tract infection, nightmare, restlessness, and oropharyngeal pain).

2. **Source:** Identify the source of the drug or biologic to be used.

Both NB and LDX will be purchased using funds awarded in this grant.

- a) Is the drug provided free of charge to subjects? ☒ YES ☐ NO

If yes, by whom? Both NB and LDX are purchased by the study PI using funds awarded in this grant.

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. Procedures for acquisition and matching of active medications to placebo are established with the Yale investigational pharmacy consistent with Dr. Grilo's current studies using pharmacological agents, including NB. For blinding, one intact active tablet will be placed in a capsule shell, back filled with sufficient quantity of microcrystalline cellulose, and closed. The capsules are visually inspected and packed. Matching placebos will be compounded, using a matching empty capsule filled with sufficient quantity of microcrystalline cellulose. The capsules are visually inspected and packed. Master formulation record and compounding record will be kept for the compounding.

Check applicable Investigational Drug Service utilized:

- ☒ YNHH IDS ☐ 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 [Courcoulas et al., 2017] and critical quantitative meta-analytic reviews [Hrabosky et al., 2006] 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. 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 [Courcoulas et al., 2013; Manning et al., 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 [Courcoulas et al., 2013]. Placebo-controlled trials of anticonvulsants topiramate and zonisamide [King et al., 2018; White et al., 2007, 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 [Grilo et al.,

2006]. SSRI antidepressants, previously regarded as a potential treatment strategy [Hrabosky et al., 2006] are characterized by small effect sizes relative to placebo [Courcoulas et al., 2013] and produce no weight loss at all [Sockalingam et al., 2017] and are inferior to CBT [Masheb et al., 2007; Devlin et al., 2016].

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

During Stage 1, participants may receive placebo for four months if randomized to placebo. During Stage 2, participants may receive placebo medication for up to 3 months if randomized to placebo.

- 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 loss-of-control 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 LOC 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 loss-of-control 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. 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. *Write here*

☒ **NO** If no, explain why this is acceptable.

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

B. DEVICES

☒ N/A

SECTION III: 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: NA

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

- | | | |
|---|--|--|
| ☒ Flyers | ☒ Internet/web postings | ☐ Radio |
| ☒ Posters | ☐ Mass email solicitation | ☐ Telephone |
| ☒ Letter | ☒ Departmental/Center website | ☐ Television |
| ☐ Medical record review* | ☐ Departmental/Center research boards | ☐ Newspaper |
| ☐ Departmental/Center newsletters | ☐ Web-based clinical trial registries | ☒ Clinicaltrials.gov |
| ☐ YCCI Recruitment database | ☒ Social Media (Twitter/Facebook): | |
| ☒ Other: JDAT; billboards | | |

* Requests for medical records should be made through JDAT as described at

<http://medicine.yale.edu/ycci/oncology/availableservices/datarequests/datarequests.aspx>

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Participants will be recruited from Yale and non-Yale-affiliated bariatric surgery centers in the United States. Recruitment methods will include social media, internet/webs postings (e.g., google ads), billboard, and flyer advertisements, as well as provider referrals. To recruit individuals who had bariatric surgery at a Yale facility, flyers, provider referral, and patient mailings will be used. Specifically, the Yale bariatric team agreed to identify potential subjects during routine medical post-surgical evaluations and support group meetings. In addition, flyers and posters alerting potential subjects to the treatment study will be placed in the Yale Gastrointestinal Surgery/Bariatric Center. Letters will be mailed to individuals who had bariatric surgery within the past 3-10 months at Yale. For the mailing, we will utilize the Yale Joint Data Analytics Team (JDAT) to identify potential subjects. JDAT creates updated list of individuals who have recently had bariatric surgery at Yale and ensures that letters are not sent to subjects who have opted out of research at Yale. Yale JDAT is able to identify potential subjects by specific parameters related to inclusion criteria such as age (18-70), and bariatric surgery (laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy) performed at Yale during the previous specified periods of time. A study flyer and letter describing the study (approved by the Yale IRB) will be mailed. If interested, individuals will have the opportunity to contact the study team for screening. *Previous experience with this recruitment process has been very successful and without adverse reactions (i.e., for NIH/NIDDK-funded bariatric trial R01 DK098492).* Participants who opted out of research will not be contacted. Our study flyers will also be posted on our program's website.

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 in-person or remote (e.g., via Zoom) 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 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. Assessment of Current Health Provider Relationship for HIPAA Consideration:

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

☐ Yes, all subjects

☒ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship. Participants had bariatric surgery at the Yale bariatric center. Some of the study team collaborators work at the Yale bariatric center and may have had contact with the participants. The principal investigator and study clinicians and assessors; however, do not have a direct existing clinical relationship with the potential subjects.

5. 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/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

- i. Describe why it would be impracticable to obtain the subject's 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. If potential participants elect to participate, they would then provide informed consent including HIPAA authorization as described at their initial visit. Visits may be done in-person or remotely.

- 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: *Write here*

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.

6. **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. 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.

7. **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.

8. **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.

NA

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 available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). 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 modification 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.

9. **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 any consent waivers

☒ Requesting a waiver of signed consent:☒ Recruitment/Screening only (if for recruitment, the questions in the box below will apply to recruitment activities only)☐ Entire Study (Note that an information sheet may be required.)**10. Use of Hospital Research Unit (HRU/CSRU)**

Participants who have not had a physical during the past year or are unable to obtain a physical from their provider, will have the option to obtain a physical through the HRU or the CSRU.

Subjects who have not had a physical in the past year and are unwilling or unable to obtain a physical from their provider will be given the option to have a physical at the CSRU or HRU. The cost of these services at the CSRU and HRU will be covered by study funds.

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO ☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:☐ Recruitment/Screening only (if for recruitment, the questions in the box below will apply to recruitment activities only)☐ Entire Study**For a full waiver of consent, please address all of the following:**

- Does the research pose greater than minimal risk to subjects?
☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO ☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?
Write here

SECTION IV: PROTECTION OF RESEARCH SUBJECTS**Confidentiality & Security of Data:**

1. 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.

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

All participants will be assigned a study ID. Subsequently, participants will be identified only by that ID. 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 ID 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.

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

4. 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?

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

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url <http://its.yale.edu/egrc> or email it.compliance@yale.edu

5. 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.

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

SECTION V: POTENTIAL BENEFITS

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

Subjects will receive potentially beneficial treatment for loss-of-control eating and weight loss. There is substantial importance in the knowledge to be gained in this study. Loss-of-control eating is associated with suboptimal outcomes after bariatric surgery and is generally associated with poorer psychosocial functioning and impairment. Finding ways to identify, understand, and improve treatments for loss-of-control eating, particularly after bariatric

surgery, is critically important to address this important health problem. The dearth of treatment research, particularly with pharmacological methods and longer-term outcomes, is strikingly at odds with the public health significance and prevalence of obesity, bariatric surgery, and disordered eating. Given the modest risks associated with the treatments and study procedures and the substantial potential knowledge to be gained, the benefit to risk ratio is very favorable.

SECTION VI: 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, interpersonal psychotherapy 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.

Subjects will be paid \$25 for the initial assessment to compensate parking and time required for the longer visit at the first assessment. Participants will also be compensated \$75 for the Stage 1 post-treatment assessment (after the four-month treatment ends), \$75 for the Stage 2 post-treatment assessment (after the three-month treatment ends), \$100 for the 6-month follow-up, and \$100 for the 12-month follow-up for a total of \$375 per subject. Our experience with numerous treatment studies has indicated that this plan with escalation in incentives over time results in a high retention rate for follow-ups which is essential for the study.

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 who recently had bariatric surgery, 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, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

- a. Will medical treatment be available if research-related injury occurs? *Write here*

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.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No ☒

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

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

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.

- a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes ☐ No ☐
- b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐
- c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered “no” to question 4a, or “yes” to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

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 submitting 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.**

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