PennState

# HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

**Protocol Title:**

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

A Double-Blind Placebo-Controlled Evaluation of Effectiveness of Oral Naltrexone in Management of Adolescent Eating Disorders

**Principal Investigator:**
Name: Rosemary Claire Roden, MD
Department: Pediatrics
Telephone: 717-531-0003 x 282916 or 717-531-1381
E-mail Address: rroden@pennstatehealth.psu.edu

**Version Date:**

Provide the date of this submission. This date must be updated each time the submission is provided to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

12/07/22

**Clinicaltrials.gov Registration #:**

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual, When do I have to register my project at ClinicalTrials.gov?" for more information.

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**Important Instructions for Using This Protocol Template:**

This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.

1. **GENERAL INSTRUCTIONS:**
   - Prior to completing this protocol, ensure that you are using the most recent version by verifying the protocol template version date in the footer of this document with the current version provided in the CATS IRB Library.
   - Do not change the protocol template version date located in the footer of this document.
   - Some of the items may not be applicable to all types of research. If an item is not applicable, please indicate as such or skip question(s) if indicated in any of the instructional text.
   - **GRAY INSTRUCTIONAL BOXES:**
     - Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.
     - **Penn State College of Medicine/Penn State Health researchers**: Delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu)**.**
     - **Penn State researchers at all other campuses**: Do NOT delete the instructional boxes from the final version of the protocol.
   - Add the completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page.

2. **CATS IRB LIBRARY:**
    - Documents referenced in this protocol template (e.g. SOP's, Worksheets, Checklists, and Templates) can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3. **PROTOCOL REVISIONS:**
    - When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.
    - Update the Version Date on page 1 each time revisions are made.

| **If you need help…** | |
|---|---|
| **University Park and other campuses:**<br>Office for Research Protections Human Research Protection Program<br>The 330 Building, Suite 205<br>University Park, PA 16802-7014<br>Phone: 814-865-1775<br>Fax: 814-863-8699<br>Email: irb-orp@psu.edu | **College of Medicine and Penn State Health:**<br>Human Subjects Protection Office<br>90 Hope Drive, Mail Code A115, P.O. Box 855<br>Hershey, PA 17033<br>(Physical Office Location: Academic Support Building Room 1140)<br>Phone: 717-531-5687<br>Email: irb-hspo@psu.edu |

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# 1.0 Objectives

| Table 1: Objectives, Endpoints, and Justifications | | |
|---|---|---|
| **Objectives** | **Endpoints** | **Justification** |
| Primary | Primary | Primary |
| Evaluate the effectiveness of oral naltrexone tablets in pediatric and adolescent eating disorders, particularly anorexia nervosa and bulimia nervosa, as compared to placebo. | ED-15 score | ED-15 is an evidenced-based metric of eating disorder symptom severity and frequency. |
| Secondary | Secondary | Secondary |
| Evaluate the effect of oral naltrexone on desire to self-harm and impulsivity in patients with eating disorders | Improvement on Eating Disorder Examination Questionnaire (EDE-Q), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Alexian Brothers Urge to Self-Injury Scale (ABUSI), and Behavioral Inhibition System/Behavioral Activation System score (BIS/BAS), need for escalation of level of care, desire to restart study article, and rate of weight restoration. | Naltrexone has some effect on desire to self-harm, and this can be examined in eating disorder patients. EDE-Q, GAD-7, PHQ- and BIS/BAS measure other features of eating disorder |
| Tertiary/Exploratory | Tertiary/Exploratory | Tertiary/Exploratory |
| none | | |

## 1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

The objective of this study is to evaluate the effectiveness of oral naltrexone tablets in pediatric and adolescent eating disorders, in particular anorexia nervosa and bulimia nervosa, as compared to placebo. The hypothesis of this study is that patients receiving oral naltrexone will demonstrate greater improvement in their score on the ED-15, an evidence-based metric of eating disorder symptom severity and frequency[1], than those receiving placebo, representing more complete recovery from eating disorder

## 1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

The primary outcome will be clinically and statistically significant reduction in ED-15 score in those receiving medication vs placebo.

### 1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Secondary outcomes will include improvement in scores on Eating Disorder Examination Questionnaire (EDE-Q)[2], the Patient Health Questionnaire-9 scale (PHQ-9,, a measure of depression)[3] the Generalized Anxiety Disorder-7 scale(GAD-7, an inventory of anxiety)[4], Alexian Brothers Urge to Self-Injure Scale (ABUSI; an inventory measuring the desire to self-harm)[5], and Behavioral Inhibition System/Behavioral Activation System score (BIS/BAS; an impulsivity inventory)[6]; need for escalation of level of care (such as requirement for early termination of partial hospitalization program to attend inpatient or residential eating disorder care or hospitalization for medical stabilization); and rate of weight restoration.

## 2.0 Background

### 2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the treatment, drug, or device is available to patient without taking part in the study.

Oral naltrexone (Revia) is a long-acting opioid antagonist with approval from the Food and Drug Administration (FDA) for treatment of alcohol use disorder and provision of opioid receptor blockade[7]. It has demonstrated some utility in treating harmful, self-stimulatory behaviors (self-injurious behavior, SIB) in patients with autism (such as head-banging, self-mutilation, etc)[8]. It is generally well-tolerated, with few side effects outside of limiting the effectiveness of opioid medication[7]. Oral naltrexone became a therapeutic agent in the context of autism with SIB related to the “opioid hypothesis” of autism, namely, that the stereotyped behaviors of autism resembled those of addiction[9,10]. There are two proposed mechanisms of action for oral naltrexone in reducing self-harming behaviors: one, naltrexone disrupts serotonergic reward pathways that reinforce SIB[11]; and two, those with SIB have chronically elevated endogenous opioid production, where SIB increases endogenous opioid activity directly[10].

There is some evidence of the value of treatment with naltrexone in bulimia[12] and binge-eating disorder [13,14], though intranasal naloxone, a related compound, has been shown to not be more efficacious than placebo in binge-eating disorder[15]. There is some evidence to suggest that naltrexone may be helpful in anorexia nervosa in adult patients[16]. A retrospective chart review of pediatric patients with bulimia did reveal subjective improvement in purging behaviors in patients taking oral naltrexone, however this study was retrospective, cross-sectional, unblinded, without a control group, and did not account for the effect of eating disorder therapy itself[17].

There is relatively little data regarding use of pharmacologic agents in anorexia nervosa, in particular in pediatric patients[14,18]. The objective of this study is to evaluate the effectiveness of oral naltrexone tablets in pediatric and adolescent eating disorders, in particular anorexia nervosa and bulimia nervosa, as compared to placebo.

### 2.2 Previous Data

Describe any relevant preliminary data.

The investigators for this specific study do not have any of their own preliminary data.

### 2.3 Study Rationale

Provide the scientific rationale for the research.

We hypothesize that oral naltrexone will provide additional treatment benefit for adolescents and young adults between age 13-25 who have compulsive behavior related to eating disorder, including bingeing, self-induced vomiting, compulsive exercise, or other inappropriate compensatory behaviors. We believe this because adult literature has demonstrated some efficacy of oral naltrexone in these areas, and pediatric autism literature has demonstrated safety in this age group.

## 3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

**Vulnerable Populations:**

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

[Do not type here]

### 3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

- Ages 13-25 (inclusive)
- Any sex
- Diagnoses of anorexia nervosa binge-purge subtype, bulimia nervosa, purging disorder, or atypical anorexia nervosa with bingeing or purging behaviors according to the Diagnostic and Statistical Manual version 5 diagnostic criteria
- Electing to participate in child or adult partial hospitalization program for eating disorder treatment at MSHMC

- The diagnostic criteria for anorexia nervosa, binge-purge subtype, are:
  A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health.

Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than minimally expected.

B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight
D. During the last three months the individual has engaged in recurrent episodes of binge eating or purging behaviour (i.e. self-induced vomiting, or the misuse of laxatives, diuretics, or enemas).[19]
E. A diagnosis of atypical anorexia nervosa can be made when the body weight is normal or high If these patients engage in bingeing or purging behaviors as defined in anorexia nervosa, binge-purge subtype, they are eligible for inclusion in this study

- The diagnostic criteria for bulimia nervosa are:
  A. Recurrent episodes of binge eating. An episode of binge eating is characterized by
  B. both:
     i. Eating in a discrete period of time (e.g. within any 2 hour period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances;
     ii. A sense of lack of control over eating during the episodes (e.g. a feeling that one cannot stop eating or control what or how much one is eating.
  C. Recurrent inappropriate compensatory behaviors to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
  D. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.
  E. Self-evaluation is unduly influenced by body shape and weight.
  F. The disturbance does not occur exclusively during episodes of anorexia nervosa.

- The diagnostic criteria for purging disorder are: recurrent purging behavior to influence weight or shape (e.g. self-induced vomiting; misuse of laxatives, diuretics, or other medications) in the absence of binge eating.

### 3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

- Diagnosis of intellectual disability
- History of known genetic or neurologic disease
- Need for treatment with opioid painkillers
- Weight <25kg
- Inability to swallow pills
- Lack of proficiency in written or spoken English
- Urine drug screen positive for opioids at enrollment
- Positive serum pregnancy test at enrollment
- Lactation
- Elevation of three times the upper limit of normal for age in either alanine aminotransferase (ALT) or asparagine aminotransferase (AST).
- High risk of suicide at enrollment on Columbia Suicide Severity Rating Scale (C-SSRS, for participants age 18)[20] or Ask Suicide Screening Questions (ASQ, participants age 13 to 17)[21]
- Current Naltrexone use

### 3.3 Early Withdrawal of Subjects

#### 3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

- New need for medical hospitalization for malnutrition or eating disorder
- Need for escalation of level of care for eating disorder, that is, requirement for inpatient or residential-level eating disorder care
- New need for opioid painkillers
- Subject consent withdrawal
- Inability to adhere to protocol requirements
- New diagnosis of pregnancy
- New elevation of three times the upper limit of normal for age in either alanine aminotransferase (ALT) or asparagine aminotransferase (AST).

#### 3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

- Patients who are withdrawn from the study will continue with their routine eating disorder care at whatever level of care is clinically appropriate for them at that time; that is, they will continue with routine care. Data generated from their participation in this study will be used to the point of their withdrawal. Specific study subjects do not require replacement.
- Patients who screen positive for opioid substances at enrollment will be provided with a referral for substance use disorder treatment.
- Patients who screen positive for pregnancy will be referred for pregnancy options counseling.

## 4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

[Do not type here]

### 4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.

- Information provided in this protocol needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form on in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, What is appropriate for study recruitment?" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

We will identify potential subjects in the Adolescent Medicine and Eating Disorders Clinic at Milton S. Hershey Medical Center. Potentially eligible participants are adolescents and young adults coming to their initial medical assessment for eating disorder evaluation. Patients who elect to attend either the child or adult Partial Hospitalization Program for Eating Disorders (PHP) who are also medically appropriate for this level of care between ages 13-25 (inclusive) will be approached at their intake appointment for recruitment and consent.

## 4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

[Do not type here]

### 4.2.1 How potential subjects will be recruited.

Potential subjects will be approached at their intake appointment or at initial psychiatry appointment for child or adult partial hospitalization program (PHP) for eating disorder, if this is the level of care they have elected to pursue. The study will be explained to them at that time and consent will be obtained, should the potential subject wish to enroll. As all participants in the study are also participating in a higher level of care for eating disorder through MSHMC, all participants are patients of either Dr Lane or Dr Essayli, who are both study team members.

### 4.2.2 Where potential subjects will be recruited.

Potential subjects will be recruited in a private therapy or medical room at the Adolescent Medicine and Eating Disorders Clinic on the second floor of the Briarcrest building.

### 4.2.3 When potential subjects will be recruited.

Potential subjects will be enrolled at one of two times: either at the initial medical screening appointment after the decision has been made for the patient to enroll in PHP, or at the initial psychiatry appointment following initial medical appointment (that is, at actual enrollment in programming).

### 4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures

**is approved by the IRB.** [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

**When patients come into the clinic for either an initial medical screening appointment for their enrollment in PHP or in the initial psychiatry appointment that they have when they enroll, a staff member will assess the patient's eligibility in participating in the research study using the information in the patient's chart and information that is obtained in the appointment.** The primary screening criterion will be that the potential subject choses to enroll. Potential subjects who are not medically appropriate for PHP or who do not desire to attend PHP will not be screened any further for the purposes of this study. The only screening that must take place is a point-of-care pregnancy test for postmenarchal (having had at least one menstrual cycle) females with amenorrhea (absent or missed menses)—which is standard of care for these patients regardless of their decision to enroll or not—and a urine drug screen, as oral naltrexone may cause immediate opioid withdrawal if administered to a person with opioid-positive urine. Potential subjects with a positive urine pregnancy test or urine drug screen positive for opioids will not be enrolled. Urine drug screen and urine pregnancy test are specifically outlined in the study consent document.

## 5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

[Do not type here]

### 5.1 Consent Process:

**Check all applicable boxes below:**

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

## 5.2 Obtaining Informed Consent

### 5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Consent and assent will take place at recruitment. Potential subjects will be recruited and enrolled at the completion of either their medical intake appointment for PHP or following the completion of their first psychiatry appointment on their first day of PHP. This will take place in a private therapy or medical room in the Adolescent Medicine and Eating Disorders Clinic, on the 2nd floor of the Briarcrest building.

### 5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Prior to initiating consent for this study, medical procedures, risks and alternative therapy should be discussed with subjects by the medical provider, as is standard of care for partial hospitalization programs for eating disorders. All inclusion and exclusion criteria should be reviewed by the medical provider to verify that the subject meets eligibility criteria prior to enrollment. Consent and assent will take place in a private, neutral environment with the patient and their parent, if the patient is under the age of 18. The study coordinator, not the principal investigator or co-investigator, will enroll the participant in the study and answer all questions. Potential patients under the age of 18 will be asked to provide assent to participate in the study; if they do not wish to provide assent then their parents cannot provide consent on their behalf and therefore "force" the child to participate. Potential subjects who plan to enroll in PHP may do so regardless of their desire to participate in this study, which will be directly told to them in plain, spoken language at time of consent/assent and enrollment, as well as written in the consent form. The decision to participate or not to participate in this study should have no impact on the clinical care the potential subject receives while they complete PHP.

## 5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

### 5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative

mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

N/A

**5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)**

N/A

**5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).**

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

**5.4.1 Indicate the elements of informed consent to be omitted or altered**

N/A

**5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements**

N/A

**5.4.3 Describe why the research involves no more than minimal risk to subjects.**

N/A

**5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.**

N/A

**5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.**

N/A

#### 5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

N/A

### 5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

#### 5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

N/A

#### 5.5.2 Describe why the research involves no more than minimal risk to subjects.

N/A

#### 5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

#### 5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

#### 5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

N/A

### 5.6 Consent – Other Considerations

#### 5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

Because the surveys used as metrics are not validated for use in non-English-speaking patients, patients who do not speak or read English as a primary language will not be enrolled.

### 5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

#### 5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

N/A

#### 5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 -SOP- Legally Authorized Representatives, Children, and Guardians."

N/A

#### 5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent

on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

N/A

### 5.6.3 Subjects who are not yet adults (infants, children, teenagers)

#### 5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Parental permission and assent will be sought at the same time from minor participants and their parents. The minor will be asked to sign, indicating their assent to participate in this project, as well as their parent will be asked to provide consent. If either party does not wish to sign or does not wish to participate in this study, they will not be enrolled and they will receive standard care in PHP.

#### 5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

All potential participants between 13 and 18 years of age will be asked to provide written assent at time of recruitment into the study, as discussed above. As discussed above, if the child does not (or cannot) provide written assent they will not be recruited, regardless of the parents' desire vis-à-vis this study. Potential participants and their parent(s) will be asked to provide written consent and assent at the same time, as above, and the consent form also includes a specific portion for written assent.

## 6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[Do not type here]

### 6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

**Check all that apply:**

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

### 6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

#### 6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

##### 6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

##### 6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

All data will be maintained in RedCAP, and will be accessible only to study members. A key linking study participants to study data will be kept for the duration that the study data are kept, and all research data will be retained per FDA regulation and institutional policy. Data maintained in PennState Health drives will be destroyed in accordance with current data management protocols at our institution and paper records will be securely shredded and incinerated.

### 6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Much of the outcomes to be studied here, including weight restoration, length of time in care, or worsening of depression, are assessed on a regular basis as a part of routine clinical care. Because participants in this study will otherwise be undergoing routine care in PHP, access to PHI would reduce need for duplicate visits for study purposes only and should increase study retention. Additionally, certain inclusion and exclusion criteria, such as lab results, will be available in PHI and help determine participant eligibility.

### 6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Because participation in this study requires negative urine drug screen and normal bloodwork prior to enrollment, without being able to evaluate PHI prior to enrollment we will not be able to determine who is eligible without duplicating studies and potentially exposing the patient to excessive risk and pain in the form of duplicate lab studies and blood draws.

## 6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

# 7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

[Do not type here]

## 7.1 Study Design

Describe and explain the study design.

This is a double-blind, randomized, placebo-controlled study. We have developed the following schedule of events. All events with a superscript ° are for study purposes only and are not part of the standard of care:

| Intervention | Pre-Enrollment Screening: Medical | Enrollment | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 (end of treatment | Week 8-9 (post-treatment) | Six Months |
|---|---|---|---|---|---|---|---|---|---|---|
| Initial Medical Assessment | x | | | | | | | | | |
| Subsequent Medical Assessment, including comprehensive review of systems | | | x | | x | | x | | x | x |
| Initial Psychiatry Assessment | x | | | | | | | | | |
| Subsequent Psychiatric Assessment, including suicidal ideation | | | x | x | x | x | x | x | x | x |
| Discussion of risks and benefits, inclusion and exclusion criteria[o] | | x | | | | | | | | |
| Consent/Assent[o] | | x | | | | | | | | |
| $25 Greenphire Clincard[o] | | x | | | | | | | | x |
| Urine Drug Screen[o] | | x | | | | | | | | |
| Serum Pregnancy Test (female participants)[o] | | x | | | | | | | | |
| Urine Pregnancy Test (female participants)[o] | | | | | x | | | x | | |
| Administer Study Article[o] | | | x | x | x | x | x | x | | |
| EKG | x | | | | | | | | | |
| AST | x | | | | x[o] | | | x[o] | | |
| ALT | x | | | | x[o] | | | x[o] | | |
| Total Bilirubin | x | | | | x[o] | | | x[o] | | |
| Direct bilirubin | x | | | | x[o] | | | x[o] | | |
| Heart Rate | x | | x | x | x | x | x | x | x | x |
| BMI | x | | x | x | x | x | x | x | x | x |
| Height | x | | x | x | x | x | x | x | x | x |
| Weight | x | | x | x | x | x | x | x | x | x |
| Blood Pressure | x | | x | x | x | x | x | x | x | x |
| Temperature | x | | x | x | x | x | x | x | x | x |
| Adverse event monitoring[o] | | | x | x | x | x | x | x | x | x |
| Suicidal Ideation Screening (ASQ for age <17or C-SSRS for age 18+) | | x | x | x | x | x | x | x | x | x |
| ED-15 | | x | x | | x | | | x | X | x |
| EDE-Q | | x | x | | x | | | x | X | x |
| ABUSI[o] | | x | x | | x | | | x | X | x |
| GAD-7 | | x | x | | x | | | x | X | x |
| PHQ-9 | | x | x | | x | | | x | X | x |
| BIS/BAS[o] | | x | x | | x | | | x | x | x |

Note: Medical assessments may occur in weeks 1,3 etc or 2,4 etc depending on standard of care for that patient. As long as patients are seen within a 14 day interval (2 week timeframe), the exact week intervals (1,3 or 2,4) may vary. Additionally, the 6 month follow up appointment may take place any time between 5-7 months after study enrollment ends.

## 7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)
- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Subjects participating in this study will receive routine care for eating disorder at a partial hospitalization (PHP) level of care at MSHMC. In PHP, all patients have biweekly medical screening visits for the duration of their time in care, as well as weekly individual therapy sessions, individual dietician sessions, and psychiatry appointments. They have supervised meals and numerous group therapy sessions. Every three weeks, patients in PHP complete a battery of mood and eating disorder indices including those evaluated in this study; participants in this study will complete an additional two surveys with this routine battery. Participants in this study will have no alterations in their routine eating disorder care outside of study article use and these additional surveys.

Subjects will be enrolled at their first visit for eating disorder programming at child or adult partial hospitalization (PHP) programming at MSHMC adolescent medicine eating disorders clinic. Informed consent/assent will be obtained as described above.

The subject will be provided with oral naltrexone or placebo weekly from the MSHMC research pharmacy. Subjects will be given one weeks' worth of medication at a time. Subjects will be randomized at enrollment to receive either study drug (naltrexone) or placebo. Participants or parents of minor participants will be provided study drug or placebo following completion of urine drug screen and consent/assent. Patients will take the medication daily while they are in programming; after completion of programming or withdrawal from the study they will no longer be given study medication. For subjects who are enrolled in child PHP and who eat meals with parents, the families may choose to administer study drug during meals at programming. For adult patients enrolled in adult programming, subjects may choose to self-administer the medication.

On their first contact with PHP, all patients in Adult PHP complete various eating disorder indices as a part of routine care, including the ED-15, PHQ-9, GAD-7, and EDE-Q. This battery of indices is repeated every 3 weeks while a patient is in programming.

For those who are enrolled in this study, they will complete their routine indices, in addition they will also complete the BIS/BAS and the ABUSI at enrollment and at weeks 1, 3, and 6 while enrolled in the study. Participants will also be asked to take the routine indices (ED-15, EDE-Q, PHQ, GAD, BIS/BAS, and ABUSI) at week 8 or 9 for a post-treatment evaluation. These will be taken in an in-person medical appointment or electronically via RedCap

6 months after enrollment, subjects will be sent copies of ED-15, EDE-Q, PHQ, GAD, BIS/BAS, and ABUSI indices either in an in-person medical appointment or via RedCap to complete. If the patient returns for medical follow-up between 5 and 7 months after enrollment, their height, weight, and body mass index will also be recorded to determine if weight restoration was maintained.

Patients in Child PHP typically complete a different inventory every three weeks as part of routine care. If a patient choses to participate in this study they will be asked to complete the same surveys as participants in Adult PHP (ED-15, GAD-7, and PHQ-9), and they will receive the same amount and type of compensation as those who already take them as part of standard of care.

REDCap, will be used to store the surveys. Participants will be sent the link to the battery of surveys via email at the designated times listed above. The link will redirect them to the programmed surveys in REDCap. Their responses will be stored in REDCap until data is exported and stored on the secure file server (hersheymed.net/files). Only authorized study personnel will have access to the REDCap surveys and folder access on the secure network.

At initial contact with the eating disorders clinic, all patients receive an initial battery of laboratory tests as a part of the standard of care for eating disorder. These tests include liver function assays and transaminase levels. Further information about liver function test and monitoring for drug-induced liver injury is outlined in section 9.0.

### 7.1.1 Enrollment.

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

As discussed above, patients can be enrolled at either their initial medical or initial psychiatric appointments for participation in the appropriate PHP for eating disorder.Per Joint Commission regulations of partial hospitalization programs for any psychiatric diagnosis, a complete blood count, blood chemistry, liver function test, urinalysis, and electrocardiogram must be obtained at enrollment and other studies at the program's discretion. If all necessary bloodwork, EKG, and urine studies have been obtained within the last two weeks, these results will be tracked down, recorded into the medical record, and any necessary and routine studies that have not been completed prior to this appointment will be completed at enrollment.

For patients enrolling at their medical appointment: after completion of the medical appointment, the study coordinator will approach the patient and family (if the patient is under 18 years of age), and discuss the study. The study coordinator will review the consent/assent forms, and after completion of the appointment the patient will be asked to obtain their routine studies (unless they have already been obtained as described above) within the coming seven days. A urine drug screen will be obtained at no cost to the participant and its results will not be placed into the medical record. Patients screening positive for any opioid will be excluded from the study and offered referral for addiction counseling. For potential female subjects, a serum pregnancy test will also be obtained at this time. Patients screening positive for pregnancy will be referred for options counseling

For patients enrolling at their psychiatric appointment: Joint Commission regulations regarding obtaining lab studies are unchanged, regardless of initial appointment location. All patients in PHP have biweekly medical appointments as a part of routine care, and routine enrollment labs are typically

obtained at the first medical appointment after first psychiatric appointment during the first seven days of programming. Labs will be ordered at that appointment and obtained within seven days, or entered into the medical record if obtained elsewhere, at that time. A urine drug screen will be obtained at no cost to the participant and its results will not be placed into the medical record. Patients screening positive for any opioid will be excluded from the study and offered referral for addiction counseling. For potential subjects who are female, a serum pregnancy test will also be obtained at this time. Patients with a positive pregnancy test will be referred for options counseling.

All participants, regardless of sex assigned at birth, gender, or menarchal status, will be required to use a highly reliable form of contraception should they be sexually active. Acceptable options have failure rates of less than 1% and include: combined hormonal contraceptives (such as oral contraceptive pills, patch, or vaginal ring), intrauterine device, depot-medroxyprogesterone injection, etonogesterel-containing implants, and progestin-only contraceptive pills. Condoms, either internal or external, are not sufficient contraception if used alone. If a participant with a birth-assigned sex of female discloses coitus while participating in the study either without the use of contraception or with contraceptive failure (such as a broken condom with no second method of contraception), the participant will be offered a prescription for emergency contraceptive (ulipristal acetate or levonorgesterel 1.5mg) within 72 hours after coitus, pregnancy testing 14 days after the episode of coitus with referral according to results, and will be withdrawn from the study.

### 7.1.2 Visit 2 or Day 2 or Post-test, etc. (If applicable)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

On the first day of study participation after enrollment, all subjects will receive a complete set of vital signs (including heart rate, blood pressure, respiratory rate, temperature, and weight) and urine drug screen including screening for opioid substances prior to receipt of their first dose of study article.

Routine care during PHP for any participant includes every-other-week in-person medical exams for the duration of the patient's stay in program, as well as frequent appointments following completion of PHP, until discharge from clinic. At each medical appointment, patients receive a comprehensive physical exam including complete vital signs as above, and are routinely asked about mood changes, physical changes, difficulty or ease of adhering to routine program protocols, etc. All patients participating in PHP complete routine surveys to assess eating disorder recovery at intake and every three weeks until completion of program. For participants in this study, the documentation of their three- and six-week appointments will be reviewed for evidence of adverse effects related to study participation by study personnel. Participants will also complete two additional surveys, the ABUSI and BIS/BAS, beyond their routine PHP surveys at weeks three, six, and eight/nine. Routine medical testing will be obtained according to clinical need at all medical visits, regardless of participation in this study, for all patients participating in PHP.

For patients participating in this study, liver function panel will be obtained once every 3 weeks at no cost to study participants for the purpose of monitoring drug safety, as well as completion of all of the relevant study indices

The vast majority of patients who require PHP have a routine medical follow-up at approximately six months; for those who do not this appointment will be made at no cost to the participant. At this appointment, participants will again undergo a comprehensive physical

exam, receive a complete set of vital signs, be interviewed on eating disorder symptomatology, and be asked to fill out study indices again and will be given a $25 Greenphire Clincard card for their time.

## 7.2 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Subjects will be enrolled in this study for a total of six months, starting at enrollment in PHP, and continuing to their final 6-month follow-up visit. They will have study interventions at 0, 3, and 6 weeks, and again at six months. They will take study medication while in PHP, and stop once six weeks of study duration is completed. Duration of PHP is individualized, but is on average about 8 weeks. Duration of PHP will not be dependent upon study participation.

## 7.3 Test Article(s) (Study Drug(s) and/or Study Device(s))

### 7.3.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

The Penn State Health IDS pharmacy will purchase Naltrexone 50mg tablets from a pharmaceutical wholesaler. The IDS pharmacy will purchase gelatin capsules and USP grade methylcellulose from a pharmacy supplier to be used for compounding the active and placebo capsules. For the active Naltrexone 50mg capsules, a Naltrexone 50mg tablet will be placed in an empty gelatin capsule with methylcellulose filler. The placebo capsules will be empty gelatin capsules filled with Methylcellulose.

The Food and Drug Administration has approved oral naltrexone for the treatment of alcohol use disorder and for blockade of opioid receptors[7]. This medication is not approved for the specific use of treatment of eating disorder, impulsive behavior, or self-injurious behavior.

### 7.3.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

All subjects receiving study medication will receive oral naltrexone 50mg oral tablets, blinded as described above. All subjects receiving placebo will receive methylcellulose, blinded as described above. All capsules, regardless of contents, will be administered by mouth once daily, at a time of day to be chosen by the study participant.

In pediatric autism literature, doses between 0.5-2 mg/kg are described[8,11,22,22–25], though in adult eating disorder literature doses of 50-100mg are described[13,14,16–18]. Food and Drug Administration labelling of oral naltrexone for treatment of alcohol use disorder and opioid receptor blockade describe an appropriate maintenance dose of 50mg per day[7]. Therefore subjects will receive 50mg of oral naltrexone a day if they are randomized to the medication group. Patients with body weight less than 25kg are excluded from the study so that no participant will exceed the maximum described pediatric dose of 2 mg/kg. Participants receiving

study article will receive 25mg of naltrexone for three days, followed by increase to study dose of 50mg/day The maximum daily dose is 50mg.

Participants will take study medication daily while they are in PHP or for six weeks total. That is, if a participant is in PHP for three weeks, they will take the study medication for the entirety of their time in PHP and then continue to take the medication for three additional weeks after discharge from PHP. If a participant is in PHP for twelve weeks—which is quite uncommon—they will only take study medication for six weeks.

For participants who complete PHP early, they will be asked to complete the same battery of surveys at 3 and 6 weeks, at weeks 8/9 for post-treatment evaluation, and at 6 months. Survey responses will be obtained via RedCAP for participants not on-site at time of survey completion.

Participants who, upon completion of the study, feel that they had significant benefit from the study article which lost upon withdrawal of the study article, are eligible for open label oral naltrexone therapy if desired. Participants will be asked at subsequent medical and behavioral health follow-up appointments if they felt they benefitted from the study article. If they feel they did, they will be offered a prescription for oral naltrexone to start at 25mg/day for three days and then 50mg a day after.

### 7.3.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

Subjects will be randomized at enrollment using RedCap. Randomization will be stratified by age (16 and under or 17 and older) and diagnosis (anorexia nervosa binge/purge subtype and bulimia nervosa or OSFED with bingeing or purging behaviors), equaling 4 strata.

### 7.3.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

Participants will receive one week of study intervention at a time, provided by Penn State Research Pharmacy. Medication will be delivered weekly to the Milton S. Hershey Medical Center Adolescent Medicine and Eating Disorders Clinic. At the time of delivery of a new week's supply of medication, participants will return any unused medication for pill counts to determine adherence.

Additionally, participants in PHP are allowed to either self-administer medication or receive medication from their parents, if under 18 years of age. Participants will have the option to take medication on-site during programming, either as self-administration if over 18 years of age or from a parent if 17 years of age or younger, as they will be in clinic for about 8 hours a day, from their own supply. No study or clinic staff will handle medication. No study or clinic staff will administer medication.

### 7.3.5 Blinding of the Test Article

Describe how the test article is blinded.

The Penn State Health IDS pharmacy will purchase Naltrexone 50mg tablets from a pharmaceutical wholesaler. The IDS pharmacy will purchase gelatin capsules and USP grade methylcellulose from a pharmacy supplier to be used for compounding the active and placebo capsules. For the active Naltrexone 50mg capsules, a Naltrexone 50mg tablet will be placed in an empty gelatin capsule with methylcellulose filler. The placebo capsules will be empty gelatin capsules filled with Methylcellulose.

### 7.3.6 Receiving, Storage, Dispensing and Return

#### 7.3.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

The Penn State Health IDS pharmacy will purchase Naltrexone 50mg tablets from a pharmaceutical wholesaler. The IDS pharmacy will purchase gelatin capsules and USP grade methylcellulose from a pharmacy supplier to be used for compounding the active and placebo capsules. For the active Naltrexone 50mg capsules, a Naltrexone 50mg tablet will be placed in an empty gelatin capsule with methylcellulose filler. The placebo capsules will be empty gelatin capsules filled with Methylcellulose.

Participants will receive seven gelatin capsules at a time, packaged in conventional amber plastic medication bottles with child safety caps. These will be brought to the Milton S. Hershey Medical Center Adolescent Medicine and Eating Disorders Clinic weekly by Penn State Research Pharmacy staff and given to participants in that setting. At time of receipt of one week's worth of study medication, any remaining medication from the previous week will be returned to the research pharmacy and disposed of by pharmacy staff according to guidelines.

#### 7.3.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

As described above, test article will be dispensed to participants or participants' parents/legal guardians in the MSHMC Adolescent Medicine and Eating Disorders Clinic. All participants in this study are also patients in PHP, therefore they all have patient identification bands while they are on-side. Participant identity will be verified with ID bands, and their legal guardians will be identified by government-issued photo identification. Participants can self-administer test-article on site during PHP, or participants' parents can administer the test article on site. While this is clearly optional and not feasible for all participants on all days—especially weekends—this method will be encouraged by study staff, though study and clinic staff will neither handle nor administer study medication.

Oral naltrexone tablets are stable at room temperature, between 20-25 degrees centigrade[7]. No specific temperature monitoring is necessary.

#### 7.3.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

Subjects will be randomly assigned to study article or to placebo as described above. The IDS pharmacy will purchase gelatin capsules and USP grade methylcellulose from a pharmacy supplier to be used for compounding the active and placebo capsules. For the active Naltrexone 50mg capsules, a Naltrexone 50mg tablet will be placed in an empty gelatin capsule with methylcellulose filler. The placebo capsules will be empty gelatin capsules filled with Methylcellulose.

The study article or placebo will be self-administered as an oral medication.

#### 7.3.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

Expired medications and medications returned by subjects unused will be documented and destroyed as per the IDS Destruction Policy. At the end of the study, any remaining study medications will be documented and destroyed as per the IDS Destruction Policy.

#### 7.3.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

Many patients in PHP are on other medications, some of which are relevant to psychiatric diagnoses—such as selective serotonin reuptake inhibitors—and several are not, such as polyethylene glycol for constipation. Medication usage will be tracked during this study by following medication reconciliation performed at biweekly medical appointments while in PHP, which is the standard of care for patients requiring this level of care.

Participants will be permitted any medication other than opioid medications. Any potential participant with a prescription for opioid medication, such as buprenorphine/naloxone combination strips or with a positive urine drug screen for opioids will be excluded. Any participant requiring opioid painkillers during this study will be dropped from the protocol. Patients will not be permitted to use medical cannabis during this study.

## 8.0 Subject Numbers and Statistical Plan

### 8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

Because this is a pilot study, we have decided *a priori* to enroll 30 participants in each arm of treatment for a total of sixty subjects. In 2019, approximately 150 patients meeting criteria for potential inclusion (between ages of 12-18, needing PHP level of care in the eating disorder clinic, no diagnosis of gender dysphoria or intellectual disability, with diagnoses of anorexia nervosa, or bulimia nervosa) were seen for initial evaluation in the eating disorder clinic. Therefore we hope to be able to enroll sixty participants over the course of 12 to 18 months.

### 8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

This is a pilot study, and enrollment size was determined *a priori* to allow for completion of enrollment within 18 months.

### 8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

For analysis, data will be analyzed for differences between participants receiving naltrexone and participants receiving placebo. The data will be analyzed for demography differences between the two groups at baseline, and outcomes will be compared at three and six weeks; as well as at 6 months. Outcomes to be compared are stated in section 1.1 and 1.2. Within each group, these outcomes will also be compared across time. Statistically significant differences between each group at each endpoint will be noted and reported.

## 9.0 Data and Safety Monitoring Plan

**This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."**

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

**Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.**

[Do not type here]

### 9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

This clinical trial will be monitored with the assistance of the Data Management Unit at Penn State Health College of Medicine. Once weekly, the principal investigator and members of the study team will review results of liver function screens, pregnancy tests, vital signs, and results of the Columbia Suicide Severity Rating Scale (C-SSRS, for participants age 18 and older ) or Ask Suicide Screening Questions (ASQ, for patients age 13 to 17)for all participants. Results of liver function tests, pregnancy tests, and vital signs will be recorded and tracked using a secured database.

It is expected that the total blood draw volume for this study will not exceed 16ml (for male participants) and 18ml (for female participants), using a volume of 4ml for measurement of hepatic function three times over nine weeks, and 1.5ml for serum pregnancy testing, with allowance for error in draw.

### 9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Participants in this study will take the study article daily while they are enrolled in program. When they complete program, they will no longer be obliged to take the study article, nor will they be required to have weekly psychiatric evaluation, laboratory evaluation, or suicide assessments. Patients in PHP have at least one medical follow-up appointment two weeks after they complete program, and further follow-up based on the patient's needs.

During the course of the trial, we will monitor:

- New diagnoses of depression, anxiety, suicidal thoughts, suicidal ideation, self-injurious behavior and related diagnoses via chart review. Monitoring for these new diagnoses is a part of routine care of PHP
- The results of every-three-weeks liver function tests
- The results of every-three-weeks urine pregnancy tests in female participants
- Vital signs
- The results of the behavioral health surveys
- New diagnoses of abdominal pain, nausea, vomiting, headache, or fatigue regardless of relationship to diagnosis of eating disorder, though these are common problems in eating disorder treatment
- New diagnoses of jaundice, liver failure, elevated transaminases, rash, or other medical problems that are uncommon in the treatment of eating disorder.
- New diagnosis of pregnancy
- Length of participation in PHP, as patients who are experiencing good results with the study article may require a shortened length of stay in program
- Need for escalation of eating disorder or mental health care, such as need for inpatient hospitalization for medical stabilization of eating disorder or other medical diagnosis, need for residential care for eating disorder,
- Incidence of death or serious bodily harm
- Incidence of acute withdrawal from narcotic agents (expected to be zero due to pre-participation urine drug screen, though this is a serious event)

### 9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

All patients participating in PHP receive biweekly medical visits, including comprehensive physical exam, vital signs, review of suicidal thoughts or behaviors, review of systems, and review of eating disorder symptom severity and frequency as a part of routine care in PHP. Patients also fill out the Columbia Suicide Severity Rating Scale (C-SSRS a metric assessing for the presence and severity of suicidality) or Ask Suicide Screening Questions (ASQ, a similar metric) once weekly while in care, with patients age 18 and older using the C-SSRS and patients age 13-17 using the ASQ. Participants in this study will be no different, with the notable exception of every-three-week liver function and urine pregnancy tests (assigned female at birth patients only).

Study participants' charts will be reviewed weekly while they are in program by the PI and the study coordinator for any of the above-mentioned possible new diagnoses, lab results, C-SSRS results, as well as review of all routine care detailed above. Study staff who provide direct care to participants will alert the PI and the study coordinator of any adverse events encountered during the course of routine care. The results of all safety screenings will be kept in a comprehensive, secure database and will be reviewed weekly by the study team

### 9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Safety data collection will begin at enrollment, as vital signs, serum pregnancy tests, and urine drug screens will be collected at that time, continue through the first medical appointment after enrollment in the study, and will be subsequently obtained at weekly intervals thereafter.

### 9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

The PI and study coordinator will review the safety data at weekly intervals with the assistance of the Data Management Unit at Penn State College of Medicine. Any adverse events deemed to be the result of study participation and not the result of routine eating disorder care will be reported to the IRB as well as the study sponsor.

### 9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

The PI and study coordinator will review the safety data at weekly intervals with the assistance of the Data Management Unit at Penn State College of Medicine. Any adverse events deemed to be the result of study participation and not the result of routine eating disorder care will be reported to the IRB as well as the study sponsor.

### 9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

No statistical tests for analyzing safety data are scheduled for this trial.

### 9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Monitoring for safety of the study article will be completed in accordance with Federal Food and Drug Administration requirements for surveillance of drug-induced liver injury (DILI), in accordance with Hy's law.

The study will be stopped early in the event of certain specific conditions that are more likely to be due to study intervention than to the disease itself. Several possible adverse effects of this medication can also be common features of eating disorder or eating disorder treatment itself, including worsening depression, self-injurious behavior, and suicide attempt [7,10,11,17,26–29]. The following circumstances would trigger immediate suspension of this study with evaluation of safety data and profile:

- Death of a study participant
- Psychiatric hospitalization for suicidal ideation in any two study participants within a six month window
- Two participants experiencing elevation of AST *or* ALT more than three times the upper limit of normal for age during the course of the study.
- AST or ALT levels elevated more than five times the upper limit of normal in any participant at any time.
- One participant with elevated serum total bilirubin to more than twice the upper limit of normal for age with evidence of pure hepatocellular injury (that is, no evidence of obstruction, malignancy, genetic disease, other medication effects, viral or bacterial infection) *and* AST or ALT elevation greater than three times the upper limit of normal for age.
- New diagnosis of liver failure of any participant
- Any other serious medical or psychiatric condition felt to be potentially related to the study article.

Any suspected case of drug-induced liver injury will be reported to the Food and Drug Administration using the specified information provided in the FDA's document, *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.*

Should any participant demonstrate elevation of AST/ALT above the upper limit of normal for age, the study article will be discontinued. AST and ALT measures will be obtained twice weekly until they have normalized. More complete history will be obtained, specifically with respect to medications, supplements, recreational drug use history, travel, and chemical exposure. Participants with elevation of AST and ALT will also be evaluated for acute viral hepatitis types A, B, C, D, and E; autoimmune hepatitis, alcoholic hepatitis, non-alcoholic steatohepatitis, biliary tract disease, and hypoxic/ischemic hepatopathy. The liver's function will be assessed directly via measurement of direct bilirubin and nternational normalised ratio (INR).

## 10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

In general, naltrexone is a well-tolerated medication, though we do plan to monitor for foreseeable risks.

Risks associated with taking oral naltrexone:

- elevated transaminases
- depression and mood changes
- abdominal pain
- nausea
- headache

Additional clinical risks that could be associated with taking Oral Naltrexone:

- Some pediatric autism literature describes low appetite or occasionally worsening of self-injurious behavior while on naltrexone[8,11,22,22–25,27]. There can also be worsening depression according to the FDA label[7]. These adverse effects are occasionally seen with PHP for eating disorder itself, and therefore we monitor for them frequently as a part of the standard of care. Should the subject or the subject's parent wish to withdraw from the study due to these effects, they are free to do so. If these adverse effects are felt to be related more to the natural history of eating disorder and not to study intervention; or the severity is minor to moderate; the subject may continue to participate in the study if desired. If the effect is severe the subject will be withdrawn.

- Oral naltrexone is a pregnancy category C medication[7], where there are animal studies that may indicate harm to the fetus but no specific human studies on this topic. For this reason, we will test for pregnancy in allbirth-assigned females at enrollment using a serum pregnancy screen, and every three weeks throughout the study using a urine pregnancy screen. . The majority of patients enrolled in child PHP have not yet had coitarche, though in adult PHP a history of sexual activity is more common.

Other risks of participation include:

- Loss of confidentiality
- Risk of randomization
- Risk of incidental findings
  Anxiety from completing questionnaires

## 11.0 Potential Benefits to Subjects and Others

### 11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 14.0.

There is potential direct benefit to participants, as the study intervention may improve eating disorder symptoms more rapidly than PHP alone.

Participants receiving placebo are not expected to have direct benefit.

### 11.2 Potential Benefits to Others

Include benefits to society or others.

Others may potentially benefit if oral naltrexone is shown to have some efficacy over PHP alone, as there are not many effective pharmacotherapies for eating disorder. If this medication is shown to have some beneficial effect in this study, the hope is that eating disorder may have another treatment option.

## 12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Any information collected as a part of standard of care will be shared with the participant and the participant's primary care provider as it would have otherwise been shared with them during PHP, usually in weekly-to-monthly letters to the primary care provider or via patient portal. This includes lab results and survey results. Any additional information obtained, such as ABUSI results or liver function tests at 6 weeks, may be shared in the same fashion.

## 13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Participants will be given a $25 Greenphire Clincard at two timepoints during the study: enrollment, and at the 6 month follow-up, for a total of $50 of reimbursement. Participants will receive the gift card shortly after their enrollment in the trial and after completing a 6 month follow up appointment. If the participant withdraws for any reason, they will only receive the $25 from enrollment.

## 14.0 Economic Burden to Subjects

### 14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

Participants are expected to incur minimal study-related costs. Any costs of routine care will be billed to their insurance providers as a part of routine care or care administered during PHP. Any costs of study-specific care, such as test article or specific laboratory evaluations, shall be covered by the study itself. Participants may incur cost related to travel for the six week and six month follow-ups. They will be compensated as described above. There is no cost to parking at the Briarcrest clinic.

### 14.2 Compensation for research-related injury

**If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.**

**If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:**
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is

available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

**For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:**
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

## 15.0 Resources Available

### 15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

Potential subjects will be recruited in a private therapy room in the Adolescent Medicine and Eating Disorders Clinic, on the 2nd floor of the Briarcrest building. Study procedures, including survey completion, will be completed in this same location. Study blood draws and urine tests will be completed at the participant's preferred outpatient laboratory as a part of standard of care; if the test ordered is specific to this study, such as a urine drug screen or the six-week LFT this will be obtained at the Penn State Children's Hospital Outpatient Laboratory.

### 15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

In 2019, approximately 150 patients meeting criteria for potential inclusion (between ages of 13-18, needing PHP level of care in the eating disorder clinic, no diagnosis of gender dysphoria or intellectual disability, with diagnoses of anorexia nervosa, bulimia nervosa, or avoidant-restrictive food intake disorder) were seen for initial evaluation in the eating disorder clinic. Therefore we hope to be able to enroll sixty participants over the course of 12 to 18 months if between 25% and 40% of patients meeting criteria choose to or are able to enroll.

### 15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

This is the principal investigator's primary research obligation and will be completed during administrative time. The principal investigator currently has six and a half clinics a week, representing weeks of six clinics in a week alternating with weeks of seven clinics. The principal investigator will complete this project in her administrative, non-clinical time.

### 15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

As the subjects are enrolled in an 8-hour-a-day program for medical and psychological care, they have ready access to medical and psychological care should they need it.

### 15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

The PI and study coordinator will have weekly meetings as discussed above; with bimonthly updates to the rest of the study team. All members of the study team are welcome to attend meetings with the PI and study coordinator

## 16.0 Other Approvals

### 16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

N/A

### 16.2 Internal PSU Committee Approvals

**Check all that apply:**

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☒ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☒ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

## 17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

### 17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

N/A

### 17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

N/A

### 17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

N/A

### 17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

N/A

### 17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

N/A

### 17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

N/A

## 18.0 Adverse Event Reporting

### 18.1 Adverse Event Definitions

| **For drug studies, incorporate the following definitions into the below responses, as written:** | |
|---|---|
| **Adverse event** | Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related |
| **Adverse reaction** | Any adverse event caused by a drug |
| **Suspected adverse reaction** | Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction".<br>• *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. |
| **Serious adverse event or Serious suspected adverse reaction** | Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. |
| **Life-threatening adverse event or life-threatening suspected adverse reaction** | An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death. |

| | |
|---|---|
| **Unexpected adverse event or Unexpected suspected adverse reaction.** | An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified. |

| **For device studies, incorporate the following definitions into the below responses, as written:** | |
|---|---|
| **Unanticipated adverse device effect** | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |

**18.2 Recording of Adverse Events**

Address the frequency and process for eliciting adverse event information from research subject, e.g., "Research subjects will be routinely questioned about adverse events at study visits."

**In the response, incorporate the following as written:**
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  **NOTE:** Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

Research subjects will be routinely questioned about adverse events at both study visits and routine care for PHP.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  **NOTE:** Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

- The test finding is considered an adverse event by the investigator.

### 18.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

### 18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

#### 18.4.1 Written IND/IDE Safety Reports

**For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:**
The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

**For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:**
The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

### 18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

**For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written**:
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

**18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB**

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

**18.6 Unblinding Procedures**

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

If unblinding becomes necessary, this can be done by submitting a request for and filling out the given unblinding form to the pharmacy. Unblinding may be necessary in the event of need for opioid painkillers, such as after MVA or other accident. Participants taking study article may not experience relief of acute pain from typical doses of opioid pain medications, therefore unblinding for appropriate pain management may be appropriate.

**18.7 Stopping Rules**

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

Monitoring for safety of the study article will be completed in accordance with Federal Food and Drug Administration requirements for surveillance of drug-induced liver injury (DILI), in accordance with Hy's law.

The study will be stopped early in the event of certain specific conditions that are more likely to be due to study intervention than to the disease itself. Several possible adverse effects of this medication can also be common features of eating disorder or eating disorder treatment itself, including worsening

depression, self-injurious behavior, and suicide attempt [7,10,11,17,26–29]. The following circumstances would trigger immediate suspension of this study with evaluation of safety data and profile:

- Death of a study participant
- Psychiatric hospitalization for suicidal ideation in any two study participants within a six month window
- Two participants experiencing elevation of AST *or* ALT more than three times the upper limit of normal for age during the course of the study.
- AST or ALT levels elevated more than five times the upper limit of normal in any participant at any time.
- One participant with elevated serum total bilirubin to more than twice the upper limit of normal for age with evidence of pure hepatocellular injury (that is, no evidence of obstruction, malignancy, genetic disease, other medication effects, viral or bacterial infection) *and* AST or ALT elevation greater than three times the upper limit of normal for age.
- New diagnosis of liver failure of any participant
- Any other serious medical or psychiatric condition felt to be potentially related to the study article.

Any suspected case of drug-induced liver injury will be reported to the Food and Drug Administration using the specified information provided in the FDA's document, *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.*

Should any participant demonstrate elevation of AST/ALT above the upper limit of normal for age, the study article will be discontinued. AST and ALT measures will be obtained twice weekly until they have normalized. More complete history will be obtained, specifically with respect to medications, supplements, recreational drug use history, travel, and chemical exposure. Participants with elevation of AST and ALT will also be evaluated for acute viral hepatitis types A, B, C, D, and E; autoimmune hepatitis, alcoholic hepatitis, non-alcoholic steatohepatitis, biliary tract disease, and hypoxic/ischemic hepatopathy. The liver's function will be assessed directly via measurement of direct bilirubin and nternational normalised ratio (INR).

# 19.0 Study Monitoring, Auditing and Inspecting

## 19.1 Study Monitoring Plan

### 19.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Describe how you will ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

The principal investigator assumes final responsibility for monitoring the safety of this study. Monitoring for adverse effects to medication will occur at all biweekly medical appointments as a part of routine care during PHP. The principal investigator will monitor the conduct of the study at regular monthly intervals.

Scores from all psychiatric measures obtained at enrollment and three weeks will be recorded in REDCap and stored on encrypted drives using minimal PHI. All Excel files will be password-protected and accessible only to study personnel. If the participant is still in PHP at the six week timepoint, psychiatric measures will be obtained and recorded in Excel as before; if the participant has completed PHP (and therefore is no longer coming to clinic on a daily basis), the participant will be emailed the study metrics via RedCap using secure email. Six month follow-up metrics will be obtained via secure email through RedCap as described for some six-week follow-ups. Their responses in RedCap will be exported to Excel and then analyzed. Lab results will also be stored in Excel using similar encryption.

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

All information will be available only to study personnel. All files will be maintained on Penn State Health drives with password protection. If study personnel needs to access the data remotely, they will need two-factor authentication for this process.

### 19.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see “WORKSHEET: Drugs (HRP-306)” and “WORKSHEET: Devices (HRP-307)”. HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Indicate the process for identifying, recording and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member’s role in the adverse event reporting process. Include the following if applicable:

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE’s.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

The principal investigator assumes final responsibility for monitoring the safety of this study. Monitoring for adverse effects to medication will occur at all biweekly medical appointments as a part of routine care during PHP. If a participant develops any observable harm that is probably related to the study articles or materials the participant will be withdrawn from the study and adverse event reporting per IRB protocol will be performed.

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA of all Unanticipated Problems/SAE's.

## 20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

[Do not type here]

### 20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

N/A

### 20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

N/A

### 20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

N/A

### 20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

N/A

### 20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

N/A

### 20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

N/A

## 21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

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## 22.0 Confidentiality, Privacy and Data Management

**IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.**

**For research being conducted at Penn State Health or by Penn State Health researchers only: The research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form Application Supplement."**

**Refer to Penn State College of Medicine IRB's "Standard Operating Procedure Addendum: Security and Integrity of Human Research Data," which is available on the IRB's website. In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all sub-sections of section 22.**

**For all other research**: complete the following section. Please refer to PSU Policy AD95 for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be carried out locally and meets applicable requirements. If you have questions about Penn State's Policy AD95 or standards or need a consultation regarding data security, please contact security@psu.edu.