TITLE: Naltrexone Treatment for Prolonged Grief Disorder: A Pilot Study

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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

List of Abbreviations

AE	Adverse Event
ACE	Acute Care of the Elderly
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
COMBINE	Combined Pharmacotherapies and Behavioral Interventions
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTSC	Clinical Translational Science Center
DARF	Drug Accountability Record Form
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICD	International Classification of Diseases
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IOS	Inclusion of the Other in the Self
IRB	Institutional Review Board
ISEL	Interpersonal Support Evaluation List
LFT	Liver Function Tests
MDD	Major Depressive Disorder
MICU	Medical Intensive Care Unit
NIH	National Institute of Health
NYP	NewYork-Presbyterian
OHRP	Office for Human Research Protections
PO	Per os (by mouth)

PG-13-R	Prolonged Grief Intensity Scale - Revised
PGD	Prolonged Grief Disorder
PHI	Protected Health Information
PI	Principal Investigator
PTSD	Post-traumatic Stress Disorder
RCT	Randomized Control Trial
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SCS	Social Connectedness Survey
SCIP	Structured Clinical Interview for PGD
SIQ	Standard Deviation
SD	Social Integration Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Tricyclic Antidepressant
USP	United States Pharmacopeia
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	Naltrexone Treatment for Prolonged Grief Disorder: A Pilot Study
Short Title:	Naltrexone Use for PGD
Clinical Phase:	IV
Principal Investigator:	Holly Prigerson, PhD
Study Description:	This is a randomized, placebo-controlled pilot study to establish the efficacy of using oral naltrexone as a pharmacological treatment for prolonged grief disorder (PGD). Participants will take their assigned medication for 8 weeks, with monthly visits to assess symptom severity, social connectedness, and adverse reactions.
Sample Size:	N_{total} = 48: $N_{naltrexone}$ = 24, $N_{control}$ = 24
Enrollment:	This study will enroll 48 subjects and screen up to 80 subjects.
Study Population:	Bereaved individuals meeting criteria for PGD who are $\geq$ 18 years old.
Enrollment Period:	12 months
Study Design:	This study will be a triple-blinded, randomized, placebo-controlled trial with a sample size of 48 participants. Monthly clinic visits will take approximately 1 hour to complete. Weekly surveys of PG-13-R will take approximately 15 minutes to complete.
Description of Sites/ Facilities Enrolling Participants:	Enrollment will take place at various NYP-WCM locations via EPIC review, flyers, referrals, and in-person recruitment.
Study Duration:	June 1, 2020 – August 31, 2021
Participant Duration:	12 weeks
Study Agent/Device Name	
Intervention Description:	Naltrexone 50 mg PO daily for 8 weeks
Primary Objective:	To determine the efficacy of naltrexone in reducing PGD symptoms compared to placebo.
Secondary Objectives:	To evaluate the effects of naltrexone on social closeness with both the decreased (source of bereavement) and the living.
Exploratory Objectives:	

- To evaluate the effects of naltrexone on social integration and social connectedness.
- To evaluate the effects of naltrexone on suicidal thoughts and behaviors.
- To evaluate the effects of naltrexone on health behaviors (e.g. alcohol and tobacco use, sleep, food consumption).
- To evaluate differences between outcomes of COVID-19-related deaths and other causes of death.

Primary Endpoints:	**PG-13-R (Grief Intensity Scale):** PGD symptoms will be measured by using PG-13-R, a self-rated scale consisting of 13

items:3 yes/no questions, and 10 Likert-scale questions. This 5-point Likert-type of measurement tool evaluates the intensity and severity of the PGD. It was shown that PG-13-R has good internal consistency among three study samples (α = .83-.93) (Prigerson et al. 2021). A symptom threshold score of 30 optimized agreement with meeting DSM symptom criteria for PGD (kappa ≥0.70 across the datasets) (Prigerson et al. 2021). Participants will be sent weekly PG-13-R surveys through email via REDcap.

Structured Clinical Interview for PGD (SCIP): This structured clinical interview is adapted to the DSM-5 criteria for PGD. Interviewers will be trained to standard which will be a $\kappa > 0.8$ agreement between trainee and trainer. Participants will be interviewed at every monthly visit.

Secondary Endpoints:

Inclusion of the Other in the Self (IOS) Scale: The IOS is a self-reported pictorial tool used to measure the subjectively perceived closeness of a relationship. The tool asks respondents to select one of seven pairs of increasingly overlapping circles that best represents their relationship with another, with more overlap signifying a closer relationship. This scale possesses good reliability, with (α = .93) for the entire sample, (α = .87) for family, (α = .92) for friendship, and (α = .95) for romantic relationships. Test-retest reliability shows similar findings, with (α = .83) for the entire sample, (α = .85) for family, (α = .86) for friendship, and (α = .85) for romantic relationships (Aron et al., 1992). This scale will be administered monthly at every visit, as well as at follow-up.

Exploratory Endpoints:

Social Integration Questionnaire (SIQ): Social Integration Questionnaire is a 10-item self-reported scale adapted from The General Social Survey distributed by the National Opinion Research Center. The participants rate the social activities they engage in and the degree of involvement of each (Tsai & Rosenheck, 2012). Questions will assess feelings and thoughts while engaged in these activities to gauge the study participant's level of social integration. Measuring social integration is important as we hypothesize that detachment from the decreased is a necessary first step towards being able to socially connect with others. In addition, social support can influence the bereavement process and thus PG-13-R scores. This scale will be administered monthly at every visit, as well as at follow-up.

Interpersonal Support Evaluation List (ISEL): Interpersonal Support Evaluation List is a 40-item self-reported interpersonal support evaluation scale (Cohen et al., 1985). The version used in this study is a shortened 16-item version adapted from the Yale Bereavement Study. The participants rate each item regarding how true or false they believe it is on a 4-point scale ranging from

"Definitely True" to "Definitely False." This survey will be administered monthly at every visit, as well as at follow-up.

Social Connectedness Survey (SCS): We have developed a brief self-reported survey for this study consisting of questions including but not limited to: assessing how much participants are socializing, who they are socializing with, and how enjoyable socializing is. This survey will be administered monthly at every visit, as well as at follow-up.

Columbia-Suicide Severity Rating Scale (C-SSRS): The CSSRS scale is a validated scale to assess suicidal behavior and ideation (Posner et al., 2011). It will be administered monthly by a trained rater at the site of all visits. This study will use 2 versions of the C-SSRS. At the Screening Visit, the baseline/screening version will be completed; for all subsequent visits the "Since Last Visit" version of the C-SSRS will be administered. The "Since Last Visit" version will also be administered online for follow-up.

If the subject screens positive for serious suicidal intent with or without a plan, they will be immediately excluded from the study, and we will have a licensed mental health professional (e.g., psychiatrist, psychologist) more fully evaluate suicidality and make arrangements for them to get to a local hospital Emergency Room if serious risk is imminent. If not at imminent risk but passive suicidal ideation was endorsed (e.g. only endorsing item 1), we will offer them referral to a licensed mental health professional.

Health Behaviors: Smoking history, alcohol history, health perception, and health promoting behaviors will be measured using the standard self-reported questionnaires validated in Yale Bereavement Study Measures monthly at every visit, as well as at follow-up.

Safety Endpoints:

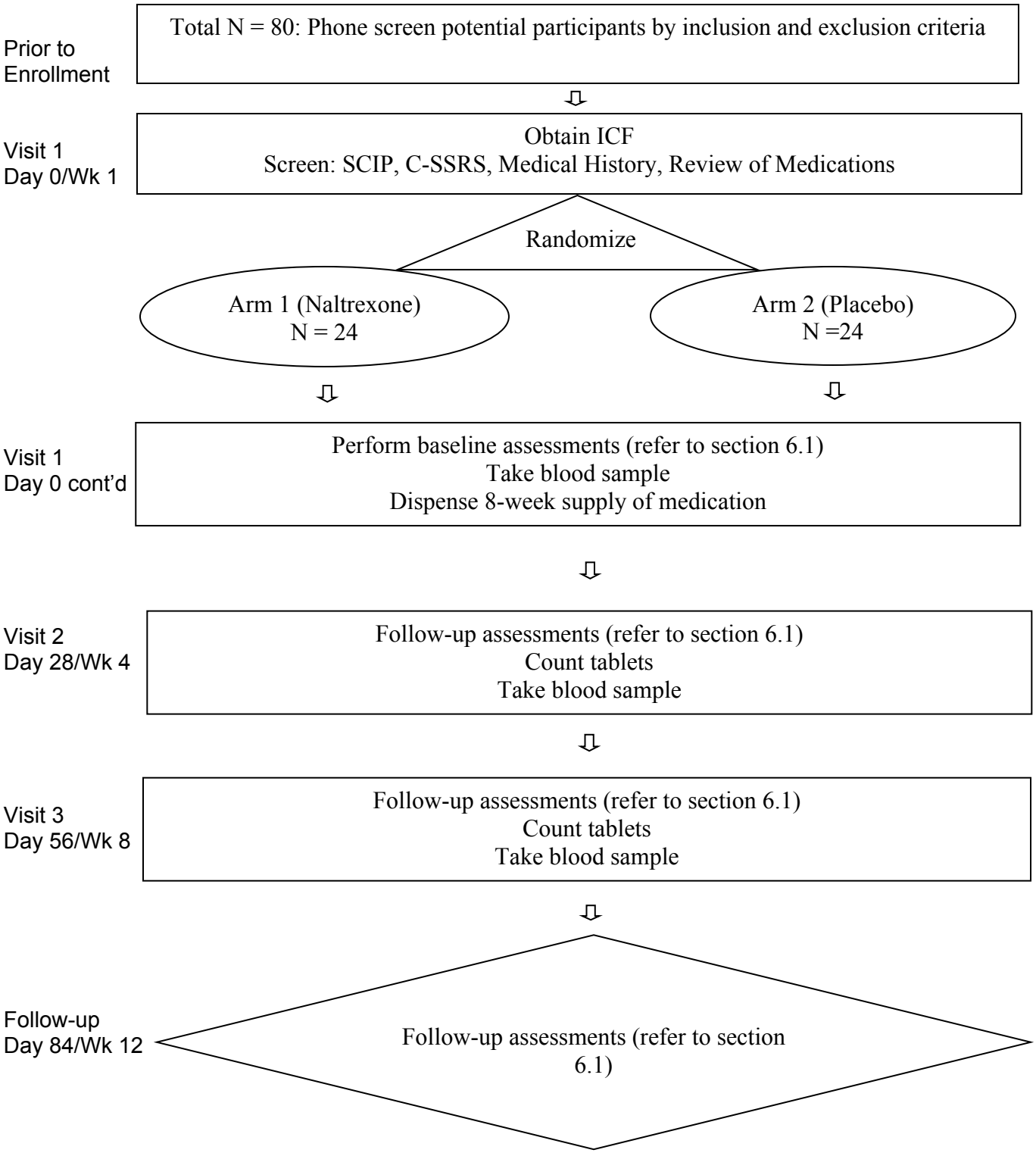
Review of Side-Effects: At the 2nd and 3rd visits, participants will be asked a nonspecific question (e.g. Have you notice any new side-effects since your last visit?) to assess whether any side-effects have been experienced since Day 1. Side-effects will be recorded on a REDCap Case Report Form (CRF) and reported to the independent medical monitor.

Laboratory tests: Laboratory tests are to screen participants for exclusion criteria and assess potential adverse effects. Blood samples will be obtained at all three-monthly visits. Laboratory tests will assess liver function tests (for bilirubin, gamma glutamyl transpeptidase, alkaline phosphatase, aspartate transaminase, alanine aminotransferase, albumin and protein). Similarly, quantitative urine pregnancy tests will be obtained at all three-monthly visits and used to determine pregnancy status. The

monthly frequency of testing has been deemed sufficient by our physician co-investigators.

One designated member of the study staff will review laboratory tests results and report any significant findings to the PI, as outlined in section 7.11.

1.1 Schema


Prior to Enrollment
Total N = 80: Phone screen potential participants by inclusion and exclusion criteria
Visit 1 Day 0/Wk 1
Obtain ICF
Screen: SCIP, C-SSRS, Medical History, Review of Medications
Randomize
Arm 1 (Naltrexone) N = 24
Arm 2 (Placebo) N =24
Visit 1 Day 0 cont'd
Perform baseline assessments (refer to section 6.1)
Take blood sample
Dispense 8-week supply of medication
Visit 2 Day 28/Wk 4
Follow-up assessments (refer to section 6.1)
Count tablets
Take blood sample
Visit 3 Day 56/Wk 8
Follow-up assessments (refer to section 6.1)
Count tablets
Take blood sample
Follow-up Day 84/Wk 12
Follow-up assessments (refer to section 6.1)

1.2 Study Objectives and End Points

1.2.1 Primary Objectives

To determine the efficacy of naltrexone in reducing PGD symptoms compared to placebo.

1.2.2 Secondary Objectives

To evaluate the effects of naltrexone on social closeness with both the decreased (source of bereavement) and the living.

1.2.3 Exploratory Objectives

- To evaluate the effects of naltrexone on social integration and social connectedness.
- To evaluate the effects of naltrexone on suicidal thoughts and behaviors.
- To evaluate the effects of naltrexone on health behaviors (e.g. alcohol and tobacco use, sleep, food consumption).
- To evaluate differences between outcomes of COVID-19-related deaths and other causes of death.

1.2.4 Primary Endpoints

PG-13-R (Grief Intensity Scale): PGD symptoms will be measured by using PG-13-R, a self-rated scale consisting of 13 items:3 yes/no questions, and 10 Likert-scale questions. This 5-point Likert-type of measurement tool evaluates the intensity and severity of the PGD. It was shown that PG-13-R has good internal consistency among three study samples (α = .83-.93) (Prigerson et al. 2021). A symptom threshold score of 30 optimized agreement with meeting DSM symptom criteria for PGD (kappa ≥0.70 across the datasets) (Prigerson et al. 2021). Participants will be sent weekly PG-13-R surveys through email via REDcap.

Structured Clinical Interview for PGD (SCIP): This structured clinical interview is adapted to the DSM-5-TR criteria for PGD. Interviewers will be trained to standard which will be a $\kappa > 0.8$ agreement between trainee and trainer. Participants will be interviewed at every monthly visit.

1.2.5 Secondary Endpoints

Inclusion of the Other in the Self (IOS) Scale: The IOS is a self-reported pictorial tool use to measure the subjectively perceived closeness of a relationship. The tool asks respondents to select one of seven pairs of increasingly overlapping circles that best represents their relationship with another, with more overlap signifying a closer relationship. This scale possesses good reliability, with (α = .93) for the entire sample, (α = .87) for family, (α = .92) for friendship, and (α = .95) for romantic relationships. Test-retest reliability shows similar findings, with (α = .83) for the entire sample, (α = .85) for family, (α = .86) for friendship, and (α = .85) for romantic relationships (Aron et al., 1992). This scale will be administered monthly at every visit, as well as at follow-up.

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One designated member of the study staff will review laboratory tests results and report any significant findings to the PI, as outlined in section 7.11.

2. Background

All text within quotation marks are taken directly from the FDA package insert.

2.1 Disease

The recent inclusion of PGD in the ICD-11 and DSM-5-TR has been a catalyst for research to advance understanding and treatment of this newly recognized mental disorder. PGD, a maladaptive response to the death of a loved one, is characterized by persistent yearning for the deceased and disabling symptoms such as emotional numbness, a sense of disbelief about the death, identity disruption, and an inability to move on and find meaning in life in the absence of the deceased. When these symptoms are functionally impairing and severe at 12 months post-loss, a person can now be diagnosed as meeting criteria for PGD.

2.2 Investigational Agent

“Naltrexone is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids…Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties… The administration of Naltrexone is not associated with the development of tolerance or dependence…Clinical studies indicate that 50 mg of Naltrexone will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours… The mechanism of action of Naltrexone in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data…Naltrexone is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Although well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%. The activity of naltrexone is believed to be due to both parent and the 6ß-naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53% to 79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and fecal excretion is a minor elimination pathway. The mean elimination half-life (T-1/2) values for naltrexone and 6-ß-naltrexol are 4 hours and 13 hours, respectively. Naltrexone and 6-ß-naltrexol are dose proportional in terms of AUC and Cmax over the range of 50 to 200 mg and do not accumulate after 100 mg daily doses.

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-ß-naltrexol occur within one hour of dosing.

The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters. In vitro tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

The systemic clearance (after intravenous administration) of naltrexone is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolized) and that extrahepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-ß-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-ß-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

The renal clearance for naltrexone ranges from 30 to 127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6ß-naltrexol ranges from 230 to 369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-ß-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling.

During two randomized, double-blind placebo-controlled 12-week trials to evaluate the efficacy of Naltrexone as an adjunctive treatment of alcohol dependence, most patients tolerated Naltrexone well. In these studies, a total of 93 patients received Naltrexone at a dose of 50 mg once daily. Five of these patients discontinued Naltrexone because of nausea. No serious adverse events were reported during these two trials.

While extensive clinical studies evaluating the use of Naltrexone in detoxified, formerly opioid-dependent individuals failed to identify any single, serious untoward risk of Naltrexone use, placebo-controlled studies employing up to fivefold higher doses of Naltrexone (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that naltrexone causes hepatocellular injury in a substantial proportion of patients exposed at higher doses

Aside from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate naltrexone, used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid-free." It is critical to recognize that naltrexone can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

A dose of 50 mg once daily is recommended for most patients. The placebo-controlled studies that demonstrated the efficacy of naltrexone as an adjunctive treatment of alcoholism used a dose regimen of naltrexone 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials**”** (Revia Package Insert 2013).

Our starting dose and regimen are consistent with those recommended by the FDA for the treatment of alcoholism.

2.3 Rationale

While psychotherapy tailored specifically for PGD has proven effective in reducing PGD symptom severity in some people (Shear et al., 2005; Bryant et al., 2014), the acute and debilitating nature of the disorder highlights the need for pharmacological treatment that can act more rapidly, may help those for whom psychotherapy may not be effective, and/or may augment psychotherapy to promote PGD symptom grief resolution. Current evidence on pharmacological intervention for PGD is scarce. One barrier to testing pharmacologic agents has been the absence of PGD as a recognized mental disorder. Based on the clinical rationale that PGD exhibits similar symptoms to MDD and PTSD, selective serotonin reuptake inhibitors (SSRIs) have been explored in three open-label trials and one case series. While these studies demonstrate moderate effectiveness in reducing grief symptoms, the results are confounded by high rates of comorbid mental disorders, and the scientific rigor has been undermined by lack of randomization and blinding, small sample sizes and low levels of statistical power (Bui et al., 2012). The other medications trialed have include tricyclic antidepressants (TCAs) and benzodiazepines, both of which have not proven effective for the reduction of symptoms of PGD (Zygmont et al.,1998; Reynolds et al,. 1999).

We believe that treating PGD as a disorder akin to MDD or PTSD is misguided, for two main reasons. The first reason is that PGD has been shown to demonstrate a distinct neural profile when compared to MDD or PTSD (Bryant et al., 2020). In contrast to conceptualizing PGD as a mood disorder such as MDD or a stress response syndrome such as PTSD, there is emerging evidence to suggest that PGD may be conceptualized as a reward dysfunction disorder, with the deceased proving the rewarding stimulus that the bereaved person craves (Kakarala et al., 2020). PGD, as noted above, is at its core a disorder of attachment and a craving and yearning for the deceased from whom they are separated (resulting in significant separation distress). In PGD, the primary gateway symptom required for diagnosis is yearning: persistent longing, pining for, or preoccupation with, the decreased. In this way, patients with PGD continue to “crave” their loved ones, even after they have died, due to the positive reinforcement provided by their memories of loved ones. The absence of the deceased creates a feeling of withdrawal – missing the person, feeling focused on his or her absence, feeling like life is not pleasurable and actually painful without the deceased, sorrow, resentment and agitation at being denied the support and security, meaning and identity the deceased provided.

A second reason for treating PGD differently is that SSRIs take weeks to months to achieve full efficacy, when those suffering from PGD would benefit from faster acting interventions, especially given significant suicide attempt risk of those meeting criteria for PGD.

Neurobiologically, numerous studies suggest that there are associations between symptoms of PGD and the reward pathway, which is the same pathway primarily responsible for addiction (Kakarala et al., 2020). The reward pathway refers to a group of interconnected structures in the brain that uses dopamine as a signal to modulate the experience of reward. Some pertinent examples of enhanced activation in brain structures in PGD that are also important to the reward pathway include the nucleus accumbens (O’Connor et al., 2008) and orbitofrontal cortex (Bryant et al., 2020).

Based on evidence supporting an association between PGD and neurobiological correlates of reward and addiction, we hypothesize that treatments for addiction might prove successful where those of MDD and PTSD have failed. Currently, disorders of addiction are treated with a wide variety of medications based upon the substance being abused, including: bupropion and varenicline for tobacco use; naltrexone and acamprosate for alcohol use; methadone and buprenorphine for opioid use (Klein 2016). Of these, we believe that naltrexone is the best medication to treat PGD when considering its mechanism of action, effects on social attachment, and side-effect profile.

Mechanistically, naltrexone is a competitive antagonist of opioid receptors. These receptors, when bound by endogenous opioids released in response to rewarding stimuli, normally cause the subsequent release of dopamine in the reward pathway. Therefore, naltrexone may be an appropriate choice to treat PGD, as its mechanism of action directly impacts the reward pathway; by blocking opioid receptors, release of dopamine in the reward pathway is inhibited. It also has two practical advantages for patients. First, it can be administered orally (daily) or intramuscularly (monthly). Second, cost of oral naltrexone is affordable, ranging from $25 to $60 per month, often covered by insurance (Stahl 2014).

Symptomatically, naltrexone targets two crucial aspects of PGD. First, assuming that having and maintaining social connections is vital to human functioning, the opioid theory of social attachment suggests that endogenous opioids are released during these experiences of social bonding, which then underlie the pleasant feelings of social bonding to positively reinforce the formation of such bonds. Based on this theory, studies have shown that naltrexone reduces feelings of social connection, especially to those closest to us (Inagaki et al., 2016; Inagaki et al., 2020). Reduced positive associations with significant others, especially the deceased, may make bereavement feel less lonely and isolated while diminishing the reward derived from reminiscing about the deceased. Second, meta-analysis confirms that naltrexone reduces craving in patients with alcohol dependence; in PGD, craving the deceased is the core symptom (Hendershot et al., 2017; Prigerson et al. 2009). Thus, naltrexone may reduce the craving for the deceased, and thereby severity of PGD. Given these findings, we predict that naltrexone will provide a pharmacological way to dampen the benefits of social bonding while reducing the yearning for or craving for the deceased loved one, which would reduce the severity of PGD.

The proposed study addresses both a conceptual and practical need regarding the treatment of PGD. Conceptually, the development of treatment for PGD is in its early stages, and studies concerning pharmacological treatment are especially lacking. Practically, patients with PGD are in dire need for a rapid, convenient, and effective intervention to promote their bereavement adjustment while diminishing the substantial risks posed by PGD for their mental and physical health and well-being.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

“After opioid detoxification, patients are likely to have reduced tolerance to opioids. As the blockade of exogenous opioids provided by naltrexone wanes and eventually dissipates completely, patients who have been treated with naltrexone may respond to lower doses of opioids than previously used, just as they would shortly after completing detoxification. This could result in potentially life-threatening opioid intoxication

(respiratory compromise or arrest, circulatory collapse, etc.) if the patient uses previously tolerated doses of opioids…There is also the possibility that a patient who is treated with naltrexone could overcome the opioid blockade effect of naltrexone...This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose.

The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Symptoms of withdrawal have usually appeared within five minutes of ingestion of naltrexone and have lasted for up to 48 hours.

Cases of hepatitis and clinically significant liver dysfunction were observed in association with naltrexone exposure during the clinical development program and in the postmarketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and postmarketing period. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the postmarketing experience with naltrexone hydrochloride used in the treatment of opioid dependence. No causal relationship has been demonstrated.

Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥ 30 mg/kg/day (180 mg/m2/day; 5 times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses ≥ 60 mg/kg/day (720 mg/m2/day; 18 times the recommended therapeutic dose, based on body surface area)… Naltrexone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus**”** (Revia Package Insert 2013).

2.4.2 Known Potential Benefits

“Naltrexone is indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. The mechanism of action of Naltrexone in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data**”** (Revia Package Insert 2013).

2.4.3 Assessment of Potential Risks and Benefits

The 7-10% of bereaving people estimated to be meet criteria for PGD have been shown to be at increased risk of medical conditions and diseases (e.g. hypertension, immunological dysfunction, cancer), substance abuse, physical and mental impairments, reduced quality of life, suicidal ideation and attempts, emergency room visits as well as multiple nights spent in the hospital (Trevino et al., 2018; Lannen et al., 2008; Prigerson et al., 1997; Holland et al., 2016; Zuckoff et al., 2006). The severe and substantial risks

posed by a PGD diagnosis highlight the need to investigate ways to help those suffering from this new mental disorder, such as pharmacologically with naltrexone.

With respect to side-effects, naltrexone is well-tolerated. The most common side-effects of naltrexone include nausea, vomiting, abdominal pain, headache, and fatigue. To monitor these side-effects, we will ask participants to report any side-effects they may experience during their monthly visits. In addition, they will be provided a phone number to report side-effects at any time during the study. The most severe side-effect warranting an FDA black-box warning is hepatotoxicity that is based on studies in which the dose of naltrexone was far greater than recommended (300 mg vs 50 mg). Furthermore, in the COMBINE study, elevations in liver function tests (LFT) were seen in only 11 of 614 participants taking naltrexone, with most normalizing after cessation and no serious long-term consequences (Anton 2008). Accordingly, participants will be monitored monthly via blood tests to assess LFTs. In addition, although naltrexone can cause sudden and severe withdrawal in opiate users, we would not trial naltrexone in bereaved individuals who are opiate users. Similarly, participants who exhibit suicidal thoughts/behaviors or are pregnant will be screened out.

The acute and debilitating nature of the disorder, in addition to the evidence demonstrating the increased risk of comorbities, highlights the need for pharmacological treatment that can act more rapidly, may help those for whom psychotherapy may not be effective, and/or may augment psychotherapy to promote PGD symptom grief resolution. A recent meta-analysis has found that naltrexone does not appear to increase the risk of serious adverse events over placebo (Bolton et al., 2019). When compared to the relative tolerability of naltrexone, it is clear that the use of this medication may yield tremendous benefits for patients with PGD not only to help them cope with the passing of a loved one, but as a preventative measure for more debilitating health issues that may arise from not treating this disorder.

2.5 Correlative Studies Background

Not applicable.

3. Study Design

3.1 Overall Design

This is a randomized, placebo-controlled, triple-blinded (to healthcare professionals, participants, and data analysts), stage IV, single-site, pilot drug trial to establish the efficacy of using oral naltrexone as a pharmacological treatment for PGD. Specifically, we hypothesize that participants receiving naltrexone will demonstrate reduced PGD symptoms (via lower PG-13-R scores) when compared to placebo. We propose to enroll 48 participants at NYP-WCM who meet criteria for PGD. Participants will be randomly assigned to the naltrexone 50 mg oral arm or placebo arm; medications will be over-encapsulated to appear identical. Participants will take their assigned medication for 8 weeks, with monthly visits assess symptom severity, social closeness, and adverse reactions. Weekly surveys of PG-13-R will be sent out to capture the temporal relationship between naltrexone use and PGD symptom severity. Follow-up 4 weeks after their last visit will assess the longevity of treatment, as well as any lingering adverse reactions.

3.2 Scientific Rationale for Study Design

Placebo was chosen as control in this study, for two reasons: (1) the presence of a placebo mitigates the placebo effect, and (2) there is a lack of treatment for PGD, meaning that most patients in real life are, by default, not receiving treatment at all (Shear et al., 2005). We propose the study design to be an RCT, because it allows us to make the trial to be one of superiority, minimizes biases, and minimizes confounding factors.

Individuals with PGD who are not treated have been shown to be at increased risk of medical conditions and diseases (e.g. hypertension, immunological dysfunction, cancer), physical and mental impairments, reduced quality of life, suicidal ideation and attempts, emergency room visits as well as multiple nights spent in the hospital.

3.3 Justification for Dose

The use of naltrexone 50 mg PO daily is consistent with that which is recommended by the FDA to treat alcoholism. Duration of 8 weeks was chosen based on our expectation that naltrexone's effects will be acute in nature, based on previous studies of naltrexone in alcoholism (Hendershot et al., 2017; Chick et al., 2000). Therefore, 8 weeks should be sufficient in duration to capture the effects of naltrexone.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last follow up-phase as shown in the Schedule of Assessments (SoA), Section 6.1.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of PGD who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. 18 years of age or older and younger than 90 years of age.
2. Lives within a reasonable distance from NYPH for convenient clinic visits.
3. Can speak, read, and write English proficiently.
4. Meet diagnostic criteria for PGD based on/consistent with the DSM criteria (American Psychiatric Association, n.d.), which includes:
    a. Death of a person the bereaved survivor considered a significant other.
    b. Since the death, there has been a grief response characterized by intense yearning/longing for the deceased person or a preoccupation with thoughts or memories of the deceased person present nearly every day for the last month.
    c. As a result of the death, at least 3 of the following symptoms have been experienced nearly every day, for at least the last month: identity disruption (e.g. feeling as though part of oneself has died); marked sense of disbelief about the death; avoidance of reminders that the person is dead; intense emotional pain (e.g., anger, bitterness, sorrow) related to the death; difficulty moving on with life

(e.g., problems engaging with friends, pursuing interests, planning for the future); emotional numbness; feeling that life is meaningless; intense loneliness (i.e., feeling alone or detached from others).

5. If a female patient, must agree to use a method of contraception and be willing and able to continue contraception during the first 8 weeks of the study while she is taking the study drug. Female patients who are planning to use oral hormonal contraception during this time must have initiated it at least 2 months prior to the baseline visit.
6. If a male patient, must agree to use a method of contraception and be willing and able to continue contraception during the first 8 weeks of the study while he is taking the study drug.

4.3 Exclusion Criteria

1. Having recently started taking/prescribed medications for any psychiatric illness (e.g. SSRIs for MDD) within the past 3 months; participants who have been taking this medication for longer than 3 months can be included.
2. Having recently started psychotherapy for any psychiatric illness within the past 3 months; participants who have been receiving psychotherapy for longer than 3 months can be included.
3. Prior history of recently active (e.g. within the past 3 months) opioid dependence.
4. Current prescription, non-prescription, or illicit opioid use, (i.e., acute use within the past 14 days or chronic use within the last 30 days), including opioid antagonists for alcohol or opioid dependence, all opioid analgesics, certain cough and cold remedies (e.g., codeine), and certain anti-diarrheal preparations (e.g., loperamide).
5. Possible future use of opioids during the study (e.g. for surgery).
6. Current use of leflunomide (Arava), droperidol (Droleptan), diazepam (Valium), thioridazine (Mellaril, Novoridazine, Thioril), or any other clinically relevant medication that has potential to cause liver injury with concurrent use of naltrexone.
7. Currently pregnant, lactating, or planning to become pregnant during the study.
8. Active hepatitis or liver disease.
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than one standard deviation (SD) above the upper limit of normal on initial laboratory examination.
10. Screen positive for active suicidal thoughts or behaviors.

4.4 Lifestyle Considerations

Not applicable.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened later. Participants may be rescreened, if, during the duration of the enrollment period, the following reasons for screen failure changes: having started a medication for psychiatric illness within the past 3 months; having started psychotherapy for psychiatric illness within the past 3 months; cessation of leflunomide, droperidol, diazepam, thioridazine or other clinically relevant medication; no longer planning to be involved a future situation that may require opioids (e.g. surgeries); no longer planning to be pregnant; no longer endorsing suicidal thoughts or behaviors. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

We predict an accrual rate of 60%, and therefore to meet the goal of enrolling N_{total} = 48, we anticipate a total screening of about 80 individuals. Recruitment methods include EPIC chart review, referrals, flyers, in-person recruitment, recruitment letters/emails, and posting online (e.g. ResearchMatch). Recruitment sources include the Cornell Center for Research on End of Life Care website, the department of Geriatrics and Palliative Medicine, the Department of Psychiatry, the Emergency Room, Medical Intensive Care Unit (MICU), local outpatient clinics (e.g. oncology, psychiatry), and local private practices (e.g. psychiatry).

Once IRB-approval is obtained, we will list the study as open online, such as on the Cornell Center for Research on End-of-Life Care website and on ResearchMatch. We also will post study recruitment fliers with bereavement support groups and relevant clinics at WCM-NYPH (e.g., the Wright Center for Aging, the Department of Geriatrics and Palliative Medicine bulletin-board; the Department of Psychiatry bulletin-board, cancer clinic bulletin-boards; Acute Care for Elderly [ACE] unit). In addition, eligible individuals based on the inclusion criteria may be identified physicians and/or staff of these departments, who will then refer them to our study; individuals may be given an “Agree to Contact” form to complete at this time to allow study staff to contact the participant first. Similarly, co-investigators may approach potential participants in WCM/NYP offices, and ask if they would be interested in the study. Trained co-investigators may either screen the participants at recruitment sites and/or ask for their contact information to be followed up at a time convenient for the potential participant. Participants may also be sent a recruitment letter/email after being identified via EPIC review for eligibility. NYP-WCM physicians may also identify potential participant patients for EPIC review. Apart from sources within the WCMC-NYP network, we will also contact outpatient psychiatry clinics and private psychiatry practices to make them aware of the study and refer patients.

Participants will be compensated $25 after each visit for a total of $100 via ClinCard.

All potential participants will be logged in a password-protected Excel file stored on a secured, shared server, which will contain their contact information, date of contact, eligibility, recruitment source, and dated of scheduled visit; identifiable health information will NOT be stored during recruitment.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not applicable.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Pre-Study	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9-11	Week 12
Phone Screen	X										
Randomization		X									
ICF		X									
C-SSRS		X			X				X		
Medical History		X									
Sociodemographics		X									
Review of Medications		X			X				X		
SCIP		X			X				X		X
IOS Scale		X			X				X		X
SIQ		X			X				X		X
ISEL		X			X				X		X
SCS		X			X				X		X
Health Behaviors Survey		X			X				X		X
Blood Sample		X			X				X		
Urine Pregnancy Test		X			X				X		
Tablet Counting					X				X		
Study Drug Dispensation		X									
Review of Side Effects					X				X		X
PG-13-R		X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluation		X	X	X	X	X	X	X	X	X	X

6.1.1 Phone Screen

Interested potential participants will contact study staff via telephone. This phone call will be used to screen participants. Study staff will briefly explain the study and confirm participant interest. Study staff will then read the inclusion and exclusion criteria to the participant; no identifiable health information will be recorded at this time**.** If the

participant confirms that they are eligible with the criteria, they will be scheduled for an initial clinic visit, preferably within the week of calling

6.1.2 Treatment Phase

Eligible subjects will be randomly assigned to naltrexone or placebo treatment groups in a 1:1 ratio using a computer-generated randomization scheme developed by the data manager.

Participants will be sent weekly PG-13-R surveys through email via REDcap. Alternatively, if requested, participants can fill this survey out over the phone.

6.1.2.1 Visit 1 (baseline; Day 0)

- SCIP
- C-SSRS
- Medical History
- ICF
- Sociodemographics
- Review of Medications
- IOS Scale
- Social Integration Questionnaire
- Interpersonal Support Evaluation List
- Social Connectedness Survey
- Health Behaviors Survey
- Blood sample (LFTs)
- Urine Pregnancy Test
- Dispense medication (8-week supply of 56 tablets)

6.1.2.2 Visit 2 (+28 days)

- SCIP
- C-SSRS
- Review of medications
- Review of side-effects
- IOS Scale
- Social Integration Questionnaire
- Interpersonal Support Evaluation List
- Social Connectedness Survey
- Health Behaviors Survey
- Blood sample (LFTs)
- Urine Pregnancy Test
- Tablet counting

6.1.2.3 Visit 3 (+28 days)

- SCIP

- C-SSRS
- Review of medications
- Review of side-effects
- IOS Scale
- Social Integration Questionnaire
- Interpersonal Support Evaluation List
- Social Connectedness Survey
- Health Behaviors Survey
- Blood sample (LFTs)
- Urine Pregnancy Test
- Tablet counting/Return medication

6.1.3 Follow-up Phase (+28 days) – administered via REDcap

- Review of side-effects
- PG-13-R
- IOS scale
- Social Integration Questionnaire
- Interpersonal Support Evaluation List
- Social Connectedness Survey
- Health Behaviors Survey

7. Study Intervention

7.1 Study Intervention/Device Description

Naltrexone HCl 50 mg is an oral medication in tablet form purchased from an FDA licensed drug wholesaler. Naltrexone will be compounded and packed into a gelatin capsule stable for 6 months at room temperature with instruction to be taken as is PO with a glass of water. Placebo will be composed of a filler material (e.g. lactose or methyl cellulose) will be identical in appearance to naltrexone via over-encapsulation.

7.2 Availability

Oral naltrexone and placebo will be supplied by Doyle's Pharmacy, located at 2425 Sunset Blvd, Houston, TX 77005.

7.3 Acquisition and Accountability

Naltrexone and all other supplies needed (gelatin capsules, filler material, etc.) will be ordered by George Handal, Compounding Pharmacist at Doyle's Pharmacy. Order for all items will be filled and delivered to Doyle's within 30 days from order date.

Phone: 713-526-1771 Fax: 713-526-1775 Cell: 832-541-9048.

Agent Inventory Records/Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all

agents/device received from Doyle's Pharmacy on a Drug Accountability Record Form (DARF) or Device Log.

7.4 Formulation, Appearance, Packaging, and Labeling

Naltrexone HCl 50 mg is a beige, round, biconvex, film-coated, scored tablet. These tablets will be over-encapsulated by a gelatin capsule. A placebo composed of filler material (e.g. lactose of methyl cellulose) encapsulated by the same gelatin capsule will be identical in appearance to naltrexone. The tablets are packaged into 60-cc white, high-density polyethylene (HDPE) bottles fitted with child-resistant closures with foil induction seals, each containing 56 tablets. Each bottle also contains a polyester coil as bottle filler.

The supplies will be labeled in accordance with all applicable guidelines and/or regulations. Bottles will be labeled as such that only pharmacists of Doyle's Pharmacy will know which ones contain naltrexone and which ones contain placebo; this information will only be shared with the PI.

The manufacture of both naltrexone and placebo will be overseen by George Handal, director of compounding for Clinical Trials at Doyle's Pharmacy.

7.5 Product Storage and Stability

Store at 20° to 25°C (68° to 77°F) in the provided container.

7.6 Preparation

A Master Formula Record is prepared based on USP 795 approved methods along with needs and requirements of study staff and participants detailing how we plan to proceed.

A Compounding Record is prepared as the product is being compounded including product name, quantity, manufacturer, lot #, Exp. Date of all supplies used. Both records are inspected, verified, signed and dated by 2 pharmacists that participated in the compounding.

Naltrexone and placebo will be packaged separately in bottles of quantities of 56 and labeled appropriately so that the pharmacy can keep track of which is which. There is no preparation needed to be done by the study staff or participants.

7.7 Dosing and Administration

All participants will take their assigned medication daily for 8 weeks, starting the day after their first visits. This medication will be dispensed once during visit 1. For naltrexone, the dose will be 50 mg. Participants will be advised to take it around lunchtime, but this is not a strict requirement; naltrexone can be taken with or without food. There is no anticipated adverse reaction from stopping naltrexone at any point in the study, therefore there is no maximum or minimum duration.

If participants miss a dose, they can resume the normal schedule the next day; there is no need to compensate for any missed doses.

7.7.1 Dosing Delays/Dose Modifications

Not applicable.

7.8 General Concomitant Medication and Supportive Care Guidelines

"Studies to evaluate possible interactions between naltrexone and drugs other than opiates have not been performed…Patients taking naltrexone may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. In an emergency situation when opioid analgesia must be administered to a patient receiving naltrexone, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged**"** (Revia Package Insert 2013).

Given that other psychiatric medications may have an effect on PGD symptom severity, concomitant use will only be allowed if the participant has been using that medication consistently for the past 3 months prior to the start of the study; otherwise, participants who do not meet this criteria will be screened out.

Concomitant use of medications known to cause liver damage, as outlined in the exclusion criteria (section 4.3), are not allowed to be used during the study due to concern of potentiated liver injury with concurrent use of naltrexone.

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment may continue for 8 weeks or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

7.10 Duration of Follow Up

Subjects will be followed for 1 week after removal from study. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

The pilot RCT is a single site, triple-blind, block-randomized study designed primarily to establish the feasibility of conducting a larger, definitive trial of the intervention and to explore the intervention's potential efficacy. It will be of 1:1 parallel group design to compare the

efficacy of naltrexone treatment in alleviating grief intensity, as measured in PG-13-R, against placebo-control group among bereaved population meeting diagnostic criteria for prolonged grief disorder.

The research statistician will use R software to generate a random sequential list of binary codes by participant number. Blocks of fixed length will be applied to keep the number of both arms relatively balanced. Set seed function will be used to ensure that the randomization schedule is reproducible. Participants having consented and passing the inclusion criteria will enter the randomization section and be assigned with the appropriate number and corresponding intervention upon confirmation.

Trial randomization codes will be kept on a password-protected Excel sheet located on a secure server. Notably, this Excel sheet itself will not contain any information pertaining to which codes correspond to which arm of treatment to maintain blinding; only the PI and Doyle's pharmacy will have this information.

Because this is a triple-blinded study, all the participants, research staffs, healthcare providers and statisticians will be blinded to the type of intervention the participant received. This level of blinding is maintained throughout the conduct of the trial, and only when the data are analyzed according to statistical analysis plan, and conclusions regarding the primary and secondary outcomes are made, will the associated personnel be unblinded.

The Principal Investigator (PI) at a site may break the blind in the event of an immediate medical emergency (e.g. SAE) or abnormal serum laboratory results (e.g. elevation in LFTs), where knowledge of the study participant's treatment assignment must be known in order to facilitate appropriate medical treatment. In these situations, the Investigator must first attempt to contact the study medical monitor before unblinding a participant's treatment identity in order to obtain concurrence that unblinding a study participant's treatment assignment is necessary. The one exception to obtaining concurrence with the medical monitor is in the event that a participant tests positive for pregnancy; if this occurs, the PI can and should immediately break the blind in order to follow the procedure laid out in section 13.1.7. If a study participant's treatment identity is unblinded by the study site, the unblinding must be documented on the CRF.

The PI is responsible for ensuring that the instructions on how to perform a code break are stored safely, that their location is known, and that access is readily available to the relevant staff in case of an emergency.

In regards to the treatment, Naltrexone HCl will be over-encapsulated with a gelatin capsule so as to be identical in appearance to placebo. Furthermore, both naltrexone and placebo will be packaged in identical bottles.

Given that naltrexone can cause elevations in LFTs, this may be a cause of imperfect blinding. However, we believe this risk is mitigated by three factors. First, based on the data from the COMBINE study showing that only 2% of participants experienced elevated LFTs, statistically it is unlikely that more than 1 participants will also experience this adverse effect in one arm (probability of even is <1.2%). Second, in cases of significant elevation in LFTs, unblinding will have to occur regardless to address this medical emergency. Third, one designated member of the study staff will review laboratory results and will be shielded from other members of the study staff. Any concerning and significant elevation will be reported to

the PI, who remains unblinded throughout the duration of the entire study. Furthermore, study staff analyzing data will not have access to these data until all other statistical analyses have been performed, where it will be used to the incidence rate.

7.12 Study Intervention/Follow-up Compliance

Adherence to protocol involves attending all visits and taking at least 80% of their medication. Three consecutive daily attempts during the week of the scheduled visit will be made to reschedule a participant's visit. Medication compliance will be evaluated by counting returned tablets; participants will be asked to bring their bottle of medication at every visit. Participants will also be asked if there was any difficulty in taking the medication during each visit. Adherence will be tracked in a drug accountability log/Excel file. Failure to meet either of these standards will result in that participant being considered "lost to follow-up".

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Criteria for discontinuing the study intervention are outlined in section 8.2. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Discontinuation of the intervention will be permanent; participants who discontinue the study intervention will not be allowed to restart the intervention at a later date.

Participants who discontinue the study intervention before their 2nd visit will be scheduled for a visit within 7 days of discontinuation to undergo the same procedures of the 3rd visit as outlined in section 6.1.2.3, and then skip to the follow-up phase 28 days after the hastened visit. Participants who discontinue the study intervention after their 2nd visit but before their 3rd visit will likewise be scheduled for a visit within 7 days of administration to undergo the same procedures of the 3rd visit as outline in section 6.1.2.3, and then proceed to the follow-up phase.

In addition to the data collected at 3rd visit as outlined in section 6.1.2.3, data to be collected at the time of study intervention discontinuation will include why the study intervention was discontinued.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time and for any reason upon request without penalty or loss of benefits to which the study participant is otherwise entitled.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance.

- If any clinical adverse event (AE), laboratory abnormality (e.g. elevated LFTs), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Participant loses medication.
- Participant lost to follow-up after 3 attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for any scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the week of their scheduled visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not applicable

10. Measurement of Effect

10.1 Response Criteria

Prolonged grief symptom severity will be evaluated by the PG-13-R scale; a decrease in symptom severity would be reflected by a lower score on the scale. More details about the PG-13-R scale can be found in section 1.2.4.

10.2 Duration of Response

Not applicable.

10.3 Progression-Free Survival

Not applicable.

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10.4 Other Response Parameters

Other endpoints used in the study are found in section 1.2.5.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the participants, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the participants or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol

amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

The pilot RCT will be a single site, triple-blind, block-randomized study to test efficacy of Naltrexone treatment in alleviating grief intensity, as measured in PG-13-R, in comparison to placebo-control group among population with prolonged grief disorder. The allocation ratio will be 1:1.

The primary outcome is participants' changes in PG-13-R scores comparing 2-month follow-up to baseline. PG-13-R is an 11-item measurement tool for Prolonged Grief Disorder (PGD) symptoms evaluation ranging from 11 to 55.

Since it is a small-scale trial, it is unlikely that there is any meaningful discouraging or encouraging primary results prior to the end of the trial. Therefore, no interim analysis will be imposed for the trial as the goal of the study is gathering evidence for efficacy/futility at the end of the study. Instead, the trial might be halted if abnormally high adverse event rate is observed (>=3 events in any arm, p=0.012).

12.2 Sample Size/Accrual Rate

The pilot RCT is designed primarily to establish the feasibility of conducting a larger, definitive trial of the intervention and to explore the intervention's potential efficacy. We, nonetheless, calculated power for the pilot RCT.

According to previous studies tracing grief intensity changes across time among the bereaved sample (Prigerson et al., 2013; Boelen et al., 2010), we estimate a natural decline of 1.0 in PG-13-R scores during a period of 2 months with a standard deviation of 6.0, for patients of 12 to 18 months post bereavement. Meanwhile, we propose a 20% decline from baseline PG-13-R (6 in scores) for treatment group. The effect size (Cohen's d) was then assumed to be 0.83. The null hypothesis is that comparing to placebo-controlled group, naltrexone treatment at 50 mg mitigates grief intensity among patients with prolonged grief disorder in a 2-month period. With 48 participants (n=24 naltrexone arm; n=24 placebo arm) and an interim analysis at 50% information fraction, we expect to have 80% power (Type II error<0.2) to detect a significant difference (Type I error <0.05) in PG-13-R baseline-to-2-month scores comparing the intervention and control groups. The accrual rate is expected to be 6 participants per month with the recruitment period spanning over 9-12 months.

12.3 Stratification Factors

No stratification factor is applicable to this single-site pilot study.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

PG-13-R baseline-to-2-month scores for each participant will be calculated as participants' PG-13-R scores at 2-month follow-up minus the scores at baseline. Two sample t-test comparing the PG-13-R baseline-to-2-month scores between intervention and control groups will be conducted as primary statistical analysis. If the normality assumption for t-test is breached, Wilcoxon rank-sum test will be used instead. In addition, multivariate linear regression model will be fitted to adjust for confounders. All statistical tests will be two-sided.

In addition to, PG-13-R baseline-to-1 month scores, PG-13-R baseline-to-3 month scores will be calculated separately. Two sample t-test comparing each type of scores between intervention and control groups will be conducted as secondary statistical analyses. If the normality assumption for t-test is breached, Wilcoxon rank-sum test will be used instead. In addition, multivariate linear regression model will be fitted to adjust for confounders.

Simultaneously, two-sample proportion test will be conducted for SCIP diagnosis at 1 month, 2 months and 3 months post baseline. If the approximation assumption for proportional test is breached, Fisher's exact test will be used instead. In addition, multivariate logistic regression model will be fitted to adjust for confounders. All statistical tests will be two-sided.

12.4.2 Analysis of Secondary Endpoints

We will first examine bivariate associations (e.g., using Pearson correlation coefficients) between the score on the IOS (in which lower scores will reflect less "integration with other" as represented by the quantified degree of circle overlap) and assignment to naltrexone vs. placebo. We also expect IOS scores to be related to reductions in PG-13-R scores and CSSRS scores of suicidal ideation and scores of greater social integration and support (SIQ and ISEL, respectively). Assuming that linear regression analyses indicate that naltrexone is significantly associated with reductions in PG-13-R scores and IOS scores, and that IOS scores are significantly associated with PG-13-R scores, we will then regress PG-13-R scores on naltrexone and IOS scores. If the effect of naltrexone loses statistical significance in relation to PG-13-R scores, then following Baron and Kenney's method of testing for mediation, it can be concluded that IOS scores (i.e., social integration) is a mediator and the mechanism through which naltrexone operates to reduce PGD symptomatology.

12.5 Interim Analysis

Since this is a small-scale trial, it is unlikely that there is any meaningful discouraging or encouraging primary results prior to the end of the trial. Therefore, no interim analysis will be imposed for the trial as the goal of the study is gathering evidence for efficacy/futility at the end of the study.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with naltrexone.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least 4 weeks' worth of naltrexone; we will conduct a secondary analysis to explore whether the treatment has an effect in a shorter time frame.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects at each monthly visit or by phone at any time, or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent (Expected Adverse Events)

The most common side-effects of naltrexone include nausea, vomiting, abdominal pain, headache, and fatigue. The most severe side-effect is hepatotoxicity. Opioid withdrawal can be sudden and severe in participants who are dependent on opioids.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Severity** of the AE:
  - Mild (Grade 1) - asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Moderate (Grade 2) - minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

  - Severe (Grade 3) - medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Life-threatening (Grade 4) - Life-threatening consequences; urgent intervention indicated.
  - Fatal (Grade 5) – Death related to AE
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Participants will undergo blood testing at every monthly clinic visit. If a participant's LFTs are found to be significantly elevated at any time, study staff will contact the participant via phone to inform them and terminate their participation in the study. At T2, T3, and T4, participants will be asked to report any new side effects that they may have experienced after starting the study. If these side effects are clinically suspected to be related to/caused by naltrexone, participants will be asked to terminate their participation in the study. Participants will also be able to contact the PI via the phone number listed on the ICF at any time to report adverse effects and may be asked to come into clinic for further evaluation and termination in the study if necessary.

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

Naltrexone is classified as a class C medication; a recent prospective cohort study of pregnant women taking naltrexone showed no adverse effects to the fetus (Towers et al., 2020). Nevertheless, participants who are pregnant will be screened out. Female participants must agree not to become pregnant and male participants must agree not to impregnate a female during the first 8 weeks of the study in which he/she will be taking the study drug; recommended methods of contraception are outlined in the consent

form. Participants who become pregnant during the first 8 weeks will be terminated from the study and will stop taking the assigned medication. Participants will then be followed for 1 week, and then asked for permission to follow to pregnancy outcome.

Additionally, female partners of male subjects will not be followed. According to the FDA package insert, naltrexone had no effect on male fertility in rats who were given 16 times the recommended therapeutic dose. There is no further evidence to suggest paternal teratogenicity.

13.2 Definition of SAE

Serious adverse events (SAEs) include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: https://research.weill.cornell.edu/sites/default/files/immediate_reporting_policy.pdf.

13.2.2 Reporting of SAE to FDA

Not applicable as this study does not require an IND. This study is exempt because: it is lawfully marketed in the United States; is not intended to be reported to FDA as a well-controlled study in support of a new indication given that this is pilot study and there is no intent to use it to support any other significant change in the labeling of the drug or advertising for the drug; does not involve a route of administration, dose, patient population, or other factors that significantly increases the risk associated with use of the drug product given that we are administering the drug based on FDA recommendations (50 mg PO).

13.2.3 Reporting of SAE to Doyle's Pharmacy

Institution will send Doyle's Pharmacy copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within 7 business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities. Copies should be faxed directly to George Handal at 713-526-1775.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study. Participants will be referred to an NYP internist for

follow-up. Research staff will then contact the participant 7 days after their appointment to confirm that AE/SAE has stabilized; if AE/SAE has not stabilized at this time, then study staff will continue to call the participant weekly until stabilization has occurred.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an AE or SAE may come to the attention of study personnel through blood tests performed at each monthly visit, urine pregnancy tests performed at each visit, interviews of a study participant during each study visit at which he/she will be asked to report adverse effects, or upon review by a study monitor. Participants will also be able to contact the PI via the phone number listed on the ICF at any time to report adverse effects. All adverse effects will be unsolicited, given that the most severe side effect will be monitored objectively via laboratory testing.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. Study staff will follow up with participants experiencing AEs 7 days after appearance of events via phone. If AEs are not resolved by then, study staff will continue to call weekly; all AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the PI within 3 days of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the PI within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

For safety, we propose using an independent medical monitor, as we believe that the risks posed to participants is low, given that naltrexone is well-tolerated. We nominate Dr. Janna S. Gordon-Elliott to serve as our medical monitor. Dr. Gordon-Elliott is an Attending Psychiatrist and Assistant Clinical Professor of Psychiatry at New York-Presbyterian Hospital/Weill Cornell Medicine. At NYP/WCM, Dr. Gordon-Elliott, a Consultation-Liaison Psychiatrist, has been active in the care of medically-ill individuals with psychiatric and behavioral conditions. Her current clinical work focuses on mental health and resilience in young adults, including college and graduate medical students. In her faculty practice, she specializes in psychotherapy and psychopharmacology, with interests in women's health, depression and anxiety, sports psychiatry, and mental health in the setting of medical illness. She has served as our psychiatry consultant for many of the clinical trials of the Center for End-of-Life Research Center.

Blood samples will be collected monthly to monitor elevations in LFTs, as hepatotoxicity is a known, but rare, severe adverse effect of naltrexone. Participants will also be asked to report any new side effects that they may have experienced after starting the study during visits. Participants

will also be able to contact the PI via the phone number listed on the ICF at any time to report adverse effects. All AEs and SAEs will be reviewed weekly to the independent medical monitor. The medical monitor's comments/review will be submitted to the IRB at the time of continuing review and submitted to participating sites upon receipt of review comments.

Adverse events that may cause the subject to terminate protocol treatment include an elevation of LFTs twice that of baseline, as well as any other adverse effects that significantly affects quality of life.

Study stopping rules are based on efficacy and safety. In regard to efficacy, the study will be terminated if the t-test statistic at interim analysis is > 3.30. In regard to safety, the study will be suspended if $\geq$3 participants in either arm are found to have significantly elevated LFTs. The PI will review these adverse events, and if these events are occurring within the naltrexone arm, then the study will be terminated. If these events are found to be occurring within the placebo arm, then those participants affected will be suspended from the study until receiving clearance from a physician.

Data gathered for this study will be obtained from interviews, questionnaires, assessments, and laboratory test results. Data collected from respondents will only be identified via a study ID that will serve as a link to identifiable information. Similarly, on CRFs or other documents submitted to outside parties, participants will be identified by no more than their participant identification number. All participant identifiable information will be kept in a password protected electronic database, REDCap. This information will also be kept in hard copy format in a locked file cabinet within a locked office and will only accessible to the study PI and relevant study staff.

Confidentiality will be ensured by removal of identifying information (name, age, gender, race/ethnicity, length of service) of participants and substituting their name with a study participant number. As noted, all data will be de-identified. Nonetheless, we will maintain a file that links subject name with the study participant number thereby enabling us to locate the study participant's research record upon request. Data will be analyzed in aggregate only, and no identities will be revealed.

Data collected will be obtained by trained and experienced research staff interviewing study participants. The data will be used specifically for the purposes outlined in this proposal and not for any other purpose. All study related documents will be stored in a secure location until the study has ended and all data analyses are complete. At that time, all study material will be placed in a secured long-term storage facility until it is deemed appropriate to destroy the study material.

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