A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Transitioning from Buprenorphine Maintenance Prior to First Dose of Vivitrol®

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CLINICAL STUDY PROTOCOL

ALK6428-A302

Study Title	A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Transitioning from Buprenorphine Maintenance Prior to First Dose of VIVITROL®
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Sponsor	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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2. SYNOPSIS

Name of Sponsor/ Company: Alkermes, Inc.	
Name of Investigational Product: Naltrexone	
Name of Active Ingredient: Naltrexone	
Title of Study: A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Transitioning from Buprenorphine Maintenance Prior to First Dose of VIVITROL®	
Investigator(s): This is a multicenter study in the United States	
Study Period: Estimated date of first subject's consent: Q2 2016 Estimated date of last subject's last visit: Q4 2017	**Phase of Development:** 3

Objectives:

Primary: To evaluate the efficacy of oral naltrexone used in conjunction with buprenorphine in adults with Opioid Use Disorder transitioning from buprenorphine maintenance prior to the first dose of VIVITROL.

Secondary: To determine the safety and tolerability of oral naltrexone used in conjunction with buprenorphine in adults with Opioid Use Disorder transitioning from buprenorphine maintenance prior to the first dose of VIVITROL.

Methodology: This Phase 3, randomized, double-blind, placebo-controlled, parallel group study will evaluate a dosing schedule for active versus placebo oral naltrexone coadministered with buprenorphine (BUP) in BUP-dependent individuals prior to first dose of VIVITROL. Eligible subjects will be randomized in a 1:1 ratio to one of 2 treatment groups (naltrexone + BUP or placebo naltrexone [PBO-N] + BUP) for induction onto VIVITROL, stratified according to low (<8 mg/day) versus high (8 mg/day) BUP maintenance dose at the time of initiation of the BUP Lead-in Period.

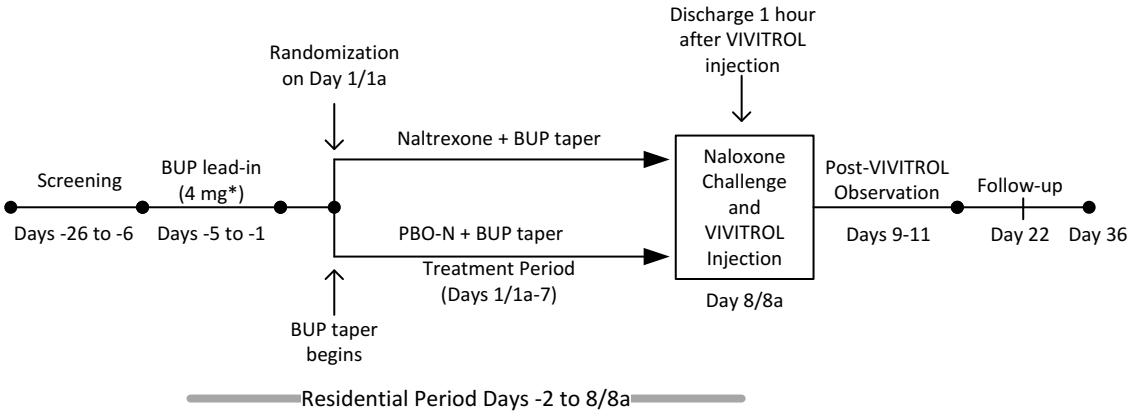
This study includes:

- BUP Lead-in Period: 5-day stabilization on 4 mg/day BUP (or less, if entry dose is lower); outpatient Days -5 through -3; residential Days -2 and -1 (option for earlier residential admission at the study clinician's discretion)
- Treatment Period: Transitional dosing with oral naltrexone or PBO-N in conjunction with BUP taper; residential Days 1/1a to 7
- VIVITROL Induction and Post-VIVITROL Observation Period:
  - A naloxone challenge and administration of VIVITROL on Day 8/8a prior to discharge
  - Post-VIVITROL outpatient monitoring (Days 9-11)

The study design is presented in the schematic below.

Evaluation of withdrawal symptoms will occur throughout the BUP Lead-in Period, the Treatment Period, and the VIVITROL Induction and Post-VIVITROL Observation Period (Days -5 through 11). Clinical testing sessions to monitor opioid withdrawal effects in response to study drug will occur on Days 1/1a through 7. Up to 2 additional study visits may be conducted (Days 1a and 8a), as needed, for subjects who do not meet criteria for proceeding with Day 1 or Day 8 procedures. In addition, subjects

will receive psychoeducational counseling, starting on Day -5 and throughout the Treatment Period, and cognitive assessments will be conducted at screening and on Days -1, 22 and 36.



*Subjects maintained on <4 mg at Day -5 will continue on their current dose until the Treatment Period taper calls for further decrease to establish a consistent daily dose prior to transitional dosing with naltrexone (see Section 8.2.1).

Number of Subjects Planned: Approximately 92 subjects are planned to be randomized; 46 subjects per treatment group.

Main Criteria for Inclusion: To be included in this study, subjects must be between 18 and 60 years of age (inclusive) at screening and be willing to provide written informed consent. Subjects must have a history of opioid use disorder diagnosis (according to criteria set forth in the Diagnostic and Statistical Manual, 5th edition [DSM-5]) for at least the prior 6 consecutive months. Subjects must have a history of prescribed BUP (or buprenorphine/naloxone [BUP/Nx]) maintenance for the prior 3 or more consecutive months and must be maintained at a dose of ≤8 mg per day for at least 30 days prior to initiating the lead-in period (Day -5; to be confirmed at screening by self-report, urine toxicology and prescription confirmation).Subjects must be voluntarily seeking treatment for opioid use disorder and be motivated to receive antagonist therapy.

Investigational Product, Dosage, Duration and Mode of Administration: Naltrexone will be administered as 2 oral doses, given at least 1 hour apart, on Days 1/1a to 7, as indicated below.

Study Day	1st Dose NTX	2nd Dose NTX
Day 1/1a	0.25 mg	0.25 mg
Day 2	0.25 mg	0.25 mg
Day 3	0.5 mg	0.5 mg
Day 4	1.5 mg	1.5 mg
Day 5	3 mg	3 mg
Day 6	7.5 mg	7.5 mg
Day 7	15 mg	15 mg

Reference Therapy, Dosage, Duration and Mode of administration: Placebo naltrexone (PBO-N) tablets will match the naltrexone drug product and will be administered as 2 oral doses, given at least 1 hour apart, on Days 1/1a to 7.

Sublingual BUP (≤4 mg) will be administered daily to all subjects during the BUP Lead-in Period (Days -5 to -1). On Days 1/1a to Day 4, the BUP dose will be tapered down to 0 mg (ie, ≤4 mg on Days 1/1a, 2 mg on Days 2-3 and 0 mg on Days 4-8/8a).

Duration of Study: The study will last approximately 9 weeks; up to 3 weeks for screening (Days -26 to -6), approximately 2 weeks for BUP Lead-In Period and Treatment Period, 4 to 5 days for VIVITROL induction and post-VIVITROL monitoring, and a 4-week follow-up period.

Criteria for Evaluation:

Efficacy:

Efficacy will be assessed via the following:

- Clinical Opiate Withdrawal Scale (COWS) score
- Subjective Opiate Withdrawal Scale (SOWS) score
- Desire for opioids using a Visual Analogue Scale (VAS)
- Patient Global Assessment of Response to Therapy (PGART)

Exploratory:

The following exploratory assessments will be conducted:

- Pupil diameter
- Quantitative Substance Use Inventory (QSUI)
- Hamilton Rating Scale for Depression (HAM-D)
- Brief Assessments of Cognition (BAC) Symbol Coding test
- Controlled Oral Word Association (COWA) task
- Wechsler Memory Scale-III Spatial Span (WMS-III SS) test
- Continuous Performance Test (CPT)
- Test of Attentional Performance (TAP)

Safety:

Safety and tolerability will be assessed via the following:

- Adverse events (AEs)
- Vital signs and oxygen saturation
- Laboratory test results
- ECG parameters
- C-SSRS score

Statistical Methods:

Efficacy:

Primary Efficacy Endpoint

- The proportion of subjects who receive and tolerate VIVITROL injection on Day 8/8a as demonstrated by mild (COWS ≤12 or SOWS ≤10) opioid withdrawal symptoms following VIVITROL administration

Key Secondary Efficacy Endpoint

- Proportion of days with COWS peak score ≤12 during the Treatment Period prior to the VIVITROL injection (Days 1/1a-7)

Other Secondary Efficacy Endpoints

- Proportion of post-VIVITROL days (Days 9-11) in which subjects in each group demonstrate mild (COWS ≤12) opioid withdrawal
- Mean peak COWS scores during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)
- Area under the curve (AUC) for COWS scores during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)
- Mean score for "desire for opioids" VAS during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)

Exploratory Endpoints

- Number and proportion of subjects in PGART response category at the end of the Post-VIVITROL Observation Period (Day 11)
- Change from baseline in pupil diameter following study drug administration during the Treatment Period (Days 1/1a-7)
- Change in frequency of substance use from screening to Day 36 assessed via the QSUI
- AUC for SOWS scores during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)
- Change from baseline in standardized T scores for cognitive assessments

Efficacy Analysis: The primary efficacy endpoint will be analyzed using logistic regression with treatment as a factor.

Safety: Reported Adverse Events (AE) terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and system organ classes. The incidence of treatment-emergent AEs will be summarized by treatment group and overall by system organ class, and preferred terms within each system organ class. Serious Adverse Events (SAEs) and AEs resulting in treatment discontinuation will also be summarized. AEs occurring during the treatment period preceding the naloxone challenge will be analyzed separately from AEs occurring on or after the naloxone challenge day.

The change from baseline in other safety parameters will be summarized by treatment group.

Concomitant medications will be categorized and presented using the World Health Organization (WHO) drug Anatomical Therapeutic Chemical (ATC) classification system.

Number and percentage of subjects initiating concomitant medications, including ancillary medications, during the induction period will be summarized.

Sample Size Considerations: The primary efficacy endpoint is the proportion of subjects who receive and tolerate VIVITROL injection on Day 8/8a as demonstrated by mild (COWS ≤12 or SOWS ≤10) opioid withdrawal symptoms following VIVITROL administration.

Assuming the proportion of subjects receiving and tolerating VIVITROL administration is 90% in Group 1 (naltrexone + BUP) and 60% in Group 2 (PBO-N + BUP), a sample size of approximately 46 subjects per treatment group will provide at least 90% power to detect a statistically significant difference between the two treatment groups at 5% level of significance in a two-sided test.

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4. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Table 2: List of Abbreviations and Definitions of Terms

Abbreviation or Term	Explanation or Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
AUC	Area under the concentration-time curve
BAC	Brief Assessments of Cognition
BUP	Buprenorphine
BUP/Nx	Buprenorphine/naloxone
COWA	Controlled Oral Word Association
COWS	Clinical Opiate Withdrawal Scale
CPT	Continuous Performance Test
CRO	Contract Research Organization
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual, 5th edition
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
EVS	Electronic vital signs
GCP	Good Clinical Practice
HAM-D	Hamilton Rating Scale for Depression
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini-International Neuropsychiatric Interview

Abbreviation or Term	Explanation or Definition
MMSE	Mini-Mental State Examination
MOTYB	Months of the Year Backward
NIDA	National Institute on Drug Abuse
NTX	Naltrexone
PBO-N	Placebo naltrexone
PGART	Patient Global Assessment of Response to Therapy
QSUI	Quantitative Substance Use Inventory
SAE	Serious adverse event
SMAST	Short Michigan Alcohol Screening Test
SOWS	Subjective Opiate Withdrawal Scale
TAP	Test of Attentional Performance
VAS	Visual Analogue Scale
WMS-III SS	Wechsler Memory Scale-III Spatial Span
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

Alkermes is developing oral naltrexone to be used in conjunction with buprenorphine (BUP) for adults with opioid use disorder prior to the first dose of VIVITROL®. Opioid use disorder is among the fastest growing substance abuse issues in the United States, which is primarily attributable to the rising rates of prescription drug abuse (Substance Abuse and Mental Health Services Administration 2013). The National Institute on Drug Abuse (NIDA) reported that over 2 million people in the United States suffer from substance use disorder related to opioid pain relievers, and in the past year 289,000 people abused heroin (National Institute on Drug Abuse 2014; Substance Abuse and Mental Health Services Administration 2014). The number of individuals with opioid use disorder continues to rise, along with corresponding increases in morbidity and mortality (Centers for Disease Control and Prevention 2011). VIVITROL, an extended release, injectable form of naltrexone, was FDA approved in 2010 for the prevention of relapse to opioid dependence, following opioid detoxification. The partial opioid agonist, BUP, has been approved since 2002 in the U.S. for office-based prescribing for the treatment of opiate dependence by preventing symptoms of opiate withdrawal. While BUP is effective for many patients, there are no studies to support the optimal duration of treatment, and therefore opioid agonist treatment is usually considered an open-ended, long-term maintenance approach. Yet some individuals, for reasons of either treatment success or treatment failure with BUP, wish to transition to become opioid-free. After an initially favorable or unfavorable response, a proportion of BUP-maintained patients leave treatment every month. Relapse is a common outcome among patients who have discontinued BUP (Ling et al, 2009; Weiss et al, 2011).

Transition to injection naltrexone represents a mechanism for protecting against relapse, but there is currently very little consensus on the best method for opioid detoxification from BUP prior to VIVITROL induction. Various opioid agonist/antagonist regimens have been proposed to minimize the severity of opioid withdrawal symptoms (Sigmon et al, 2012). A common component of many regimens is the use of low doses of naltrexone to shorten the withdrawal period. However, there are no clear guidelines or standards on how to successfully manage patients during the transition period from BUP to VIVITROL, or on the appropriate length of this transition. Establishing a reproducible regimen to transition patients from BUP maintenance to VIVITROL treatment represents an important clinical goal.

Current prescribed treatments for opioid dependence, including VIVITROL, may be implemented in an inpatient or outpatient facility. Due to the rising costs of inpatient treatment as well as patient preference, an increasing number of providers are initiating treatment in an outpatient setting (Day et al, 2005). However, outpatient treatment is not without its challenges; rates of completion tend to be low and rates of relapse to opioid use following detoxification are high (Day et al, 2005). Kleber et al. reported that approximately 80% of patients relapse during outpatient detoxification without transition to medication-assisted treatment (Kleber 2007), which can be partly attributed to patients' strong desire for opioids as well as experiences of intolerable withdrawal symptoms including gastrointestinal stress, pain, anxiety and insomnia. One recent study comparing rates of outpatient induction onto VIVITROL for opioid-dependent patients found that a regimen combining ascending doses of oral naltrexone with a brief

decreasing BUP taper demonstrated superiority to a standard BUP-assisted detoxification (56.1% versus 32.7%; χ_1^2=6.58, p=0.010). These results support the safety, efficacy and tolerability of low-dose naltrexone, in conjunction with brief BUP dosing and adjunctive non-opioid medications, for initiating adults with opioid dependence onto VIVITROL (Sullivan et al, 2016).

While agonist maintenance is protective against opioid withdrawal, the question of how long patients should be maintained on BUP to provide adequate protection against relapse is of considerable clinical relevance. Several studies have found that for heroin or prescription opioid users initially transitioned to BUP, rates of relapse are high after stabilization for 4 weeks followed by 7- or 28-day taper (Nielsen et al, 2013). Previous trials have noted high relapse rates following BUP stabilization periods of up to 3 months. In a multi-site CTN trial, following 4 weeks of BUP/naloxone maintenance with flexible dosing, only 44% of patients were opioid-free at its completion. At 1-month follow-up, the percentage of abstinent patients who had undergone either taper condition had fallen to 18% (Ling et al, 2009). Another recent study examined the efficacy of brief vs. extended BUP/naloxone treatment, with differing counseling intensities, for patients dependent on prescription opioids. Weiss et al. (2011) found that more than 90% of patients relapsed after an initial 3-week taper; following re-stabilization for 12 weeks, over 90% of patients again relapsed when tapered off BUP/naloxone, even in patients receiving counseling in addition to standard medical management (Weiss et al, 2011). However, there has been little research on the outcome of patients tapered off BUP after longer periods of stabilization, nor on methods to reduce the risk of relapse after tapering off BUP.

5.2. Study Rationale

Developing a strategy to assist patients in safely tapering from BUP by induction onto antagonist therapy has immediate clinical relevance, as safely transitioning patients off BUP would enable more opioid-dependent patients to access treatment. In areas of the country where BUP providers have reached maximal federally permissible limits of prescribing for 100 patients, opioid-dependent individuals seeking treatment may face waiting lists. While some patients who wish to discontinue BUP after years of stability are unable to discontinue because of attendant opioid withdrawal, others seeking induction cannot be accommodated and bear the risks of ongoing opioid abuse, including overdose, risk of contracting hepatitis B or C or HIV, needing to resort to crime to support the habit, and so forth. In addition, as of May 2013, 11 states have imposed lifetime limits on prescriptions of BUP for the treatment of opioid dependence, ranging from 12 months to 36 months (Rinaldo et al, 2013). Finally, given the stigma associated with chronic maintenance on opioid substitution, development of an effective strategy to assist patients in safely transitioning from BUP to injection naltrexone is important and could help attract more patients into treatment.

5.3. Rationale for Selection of Dosing Regimen

Mannelli et al. reported findings from an open-label study evaluating the use of low doses of oral naltrexone, in addition to BUP and ancillary medications, to safely transition subjects from opioid dependence to VIVITROL treatment (Mannelli et al, 2014). The regimen used in this study was based upon prior clinical experience wherein low doses of naltrexone, combined with a methadone taper, reduced the severity of withdrawal symptoms during inpatient detoxification (Mannelli et al, 2003; Mannelli et al, 2009; Mannelli et al, 2012). Subjects (N=20) were given

increasing doses of naltrexone during a 7-day outpatient period, in conjunction with 3 days of BUP. Withdrawal discomfort, craving, drug use and adverse events (AEs) were assessed daily until the administration of VIVITROL on Day 8. Adverse events were assessed weekly over the following month. Fourteen of the 20 subjects received VIVITROL, and 13 subjects completed all subsequent safety assessments. Withdrawal discomfort, craving and opioid or other drug use were significantly lower during the detoxification/induction period and after VIVITROL administration, when compared with the assessments administered at pretreatment baseline. No serious AEs (SAEs) occurred. The 7-day outpatient regimen using low doses of naltrexone, in combination with BUP, in patients with opioid use disorder prior to induction to VIVITROL was reported to be safe and well tolerated. The current study design is based on the regimen described in Mannelli's recent study (Mannelli et al, 2014).

Recruitment of a clinical population maintained at a BUP dose of ≤8 mg/day at study entry supports tolerability of the transition from opioid agonist maintenance, while increasing generalizability. Since BUP doses of <8 mg/day yield <80% μ-opioid receptor occupancy (Greenwald et al, 2003) and increase risk of relapse (D'amore et al, 2012), these doses require clinical management within the protocol (ie, BUP Lead-in phase). In light of difficulty tapering to doses below 8 mg BUP (Ling et al, 2009), this study includes 2 days of residential monitoring of BUP 4 mg/day to confirm tolerability via Clinical Opiate Withdrawal Scale (COWS)/Subjective Opiate Withdrawal Scale (SOWS) prior to randomization.

Findings from a recent open-label pilot study (Dakwar and Kleber 2015) support the safety and tolerability of the proposed regimen for BUP-dependent individuals transitioning to VIVITROL during a 7-day inpatient stay. In that investigation, subjects who had tapered to 2 mg daily of BUP took their final dose on the day of admission (Day 1). On Day 3, they received 6.25 mg naltrexone and then received ascending doses on Days 4 through 6 (12.5, 25, 50 mg). Subjects who tolerated the 50 mg dose of oral naltrexone received 380 mg VIVITROL by intramuscular injection on Day 6. Adjuvant medications included clonidine, clonazepam, zolpidem, ibuprofen and loperamide. Investigators found that 100% (6/6) of subjects were able to transition to VIVITROL, and subjects exhibited a significant decrease in SOWS scores ($p=0.043$) during this period. The approach used by Dakwar and Kleber (Dakwar and Kleber 2015) for transitioning BUP-dependent adults is largely consistent with that outlined by Sigmon et al. (Sigmon et al, 2012), who summarized clinical practices for transitioning patients from short-acting opioid agonists to naltrexone: namely, the combined use of BUP, oral naltrexone and ancillary medications to manage opioid withdrawal symptoms.

6. OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of oral naltrexone used in conjunction with buprenorphine in adults with Opioid Use Disorder transitioning from buprenorphine maintenance prior to the first dose of VIVITROL.

6.2. Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of oral naltrexone used in conjunction with buprenorphine in adults with Opioid Use Disorder transitioning from buprenorphine maintenance prior to the first dose of VIVITROL.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Each subject must meet all of the inclusion and none of the exclusion criteria to be qualified to participate in this study.

7.1. Subject Inclusion Criteria

1. Is willing and able to provide written informed consent
2. Is willing and able to provide government issued identification. If government issued identification does not contain a photo, a second form of photo identification will be required.
3. Is between 18 and 60 years of age, inclusive, at screening
4. Has a body mass index (BMI) of 18.0 to 40.0 kg/m^2, inclusive, at screening
5. Has a history of Diagnostic and Statistical Manual, 5th edition (DSM-5) diagnosis of opioid use disorder for at least the prior 6 consecutive months
6. Has a history of prescribed BUP (or buprenorphine/naloxone [BUP/Nx]) maintenance for the prior 3 or more consecutive months and is currently BUP-maintained, as confirmed by the following:
   - Self-reported daily BUP maintenance
   - Urine toxicology positive for BUP
   - Confirmation of prescription by:
     – Inspection and/or accessing electronic Prescription Monitoring Program registry; and/or
     – Direct contact with BUP provider
7. Has been maintained on a daily BUP dose of ≤8 mg* for at least 30 days prior to Day -5 (initiation of the BUP Lead-in Period)

   * BUNAVAIL® 4.2 mg or ZUBSOLV® 5.7 mg has bioequivalence to 8 mg of generic BUP (Biodelivery Sciences International Inc 2014; Orexo Us Inc 2013-07)
8. Is voluntarily seeking treatment for opioid use disorder and has a desire or motivation for antagonist therapy
9. Is willing to abide by the contraception requirements for the duration of the study (please refer to Section 8.9.4 for additional details regarding contraception)
10. Is willing to provide written consent to allow the study physician to confer with the BUP provider, concerning the subject's interest in transitioning to VIVITROL

7.2. Subject Exclusion Criteria

1. Is pregnant (ie, has a positive pregnancy test) or breastfeeding at screening or Day -5 or is planning to become pregnant during the study period
2. Has a positive urine drug screen for methadone at screening or Day -5

3. Has a positive urine drug screen for opiates or oxycodone at screening or Day -5
4. Has used naltrexone (oral or VIVITROL) within the 90 days prior to Day -5
5. Has used methadone within the 30 days prior to Day -5
6. Has a history of seizures (with the exception of febrile seizures), or has received anticonvulsant therapy during the past 5 years for treatment of seizures (use of anticonvulsant during past detoxification is not exclusionary)
7. Has a condition, disease state, previous medical history or observed abnormalities (including physical examination, electrocardiogram [ECG], laboratory evaluation [eg, kidney or liver function test result] or urinalysis finding) at screening that, in the opinion of the investigator, would preclude safe participation in the study or interfere with the study assessments, including, but not limited to, the following:
    - Uncontrolled hypertension, uncontrolled diabetes, renal disease/impairment, stroke or neurological disorder, AIDS indicator disease, cardiovascular (eg, endocarditis), neoplastic disease (excluding adequately treated skin cancer or carcinoma in situ of the cervix), chronic pain condition requiring ongoing opioid analgesia
    - Aspartate aminotransferase or alanine aminotransferase value ≥3 times the upper limit of normal
    - Treatment for an active TB infection
    - Oral cavity pathology that would interfere with sublingual absorption
    - Significant hypotension below 90/60 and pulse below 60 bpm
    - Any contraindicated medical condition per the approved labeling for either BUP or naltrexone
8. Has any of the following psychiatric conditions per DSM-5 criteria, as assessed by the MINI:
    - Diagnosis of schizoaffective disorder or bipolar disorder; or current, untreated or unstable major depressive disorder (subjects with current, but stable depression, depressive symptoms or major depressive disorder may be eligible provided bipolar disorder and schizoaffective disorder have been ruled out)
    - Diagnosis within the past 12 months of other psychiatric conditions or disorders that, in the investigator's opinion, could interfere with participation in the study
9. Is currently physiologically dependent on any psychoactive substance (except opioids, caffeine or tobacco) requiring medical intervention for detoxification
    - Breathalyzer alcohol test positive at Day -5 will be exclusionary; a positive breathalyzer test during screening may be repeated, provided that one negative test is obtained by Day -5
    - Benzodiazepine dependence will be confirmed by positive urine drug screen and investigator judgment during screening

10. Has a history of hypersensitivity or adverse reaction to BUP, naltrexone, VIVITROL or naloxone
11. Has a history of more than 3 unsuccessful inpatient or medically assisted outpatient opioid detoxifications during the subject's lifetime
12. Has had significant suicidal ideation or behavior within the past year, confirmed by a baseline Columbia-Suicide Severity Rating Scale (C-SSRS) response of "Yes" to questions 4 or 5
13. Is currently participating in or has participated in a clinical trial of an investigational drug, device or biologic, within 3 months prior to screening
14. Has a history of accidental drug overdose (defined as an episode of opioid-induced unconsciousness or incapacitation) in the past 12 months, whether or not medical treatment was sought or received
15. Is court mandated to receive treatment for opioid use disorder
16. Is employed by the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or immediate family* member of the employees or the investigator
17. Is employed by the sponsor or contract research organization (CRO; permanent, temporary contract worker or designee responsible for the conduct of the study), or immediate family* member of a sponsor or CRO employee

    * Immediate family is defined as a spouse, parent, sibling or child, whether biological or legally adopted.

7.3. Subject Withdrawal

Subjects who initiate screening but are not randomized will be considered screen failures. A subject who has previously screen failed may be allowed, at Investigator discretion, to repeat the screening process, provided that the circumstance that led to screen failure is no longer present. A randomized subject who is eligible to receive the naloxone challenge will be considered a treatment completer. Subjects completing all visits during the follow-up period will be categorized as completing the study.

A subject may be discontinued from the study at any time if it is not in the subject's best interest to continue or he/she chooses to withdraw. Reasons for subject withdrawal include:

- AE
- Lack of efficacy
- Withdrawal by subject
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Study terminated by sponsor

- Other

If a subject withdraws or is withdrawn from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the investigator or until the subject is deemed by the investigator to be lost to follow-up. If, in the opinion of the investigator, it is necessary to monitor a subject beyond the last safety follow-up visit, the follow-up period may be extended as necessary. In such instances, the sponsor and the investigator will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. The subject should be encouraged to return to the study center for an early termination (ET) visit, as close as possible to the subject's date of study withdrawal. The ET visit will match the procedures at Day 9 (Table 4). If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject in order to assess as many safety parameters as possible. All data collected remotely must be documented and kept in the subject's record.

The investigator must maintain a record of all subjects who fail to complete the study. The reason for study discontinuation will be entered on the appropriate electronic case report form (eCRF). A subject will be deemed lost to follow-up after 3 attempts at contact have been made. The third attempt at contact must be a certified letter accompanied by a survey inquiring the reason for study discontinuation. All attempts at contact will be documented.

7.4. Replacement of Subjects

Randomized subjects who withdraw prior to the completion of the study will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This Phase 3, randomized, double-blind, placebo-controlled, parallel group study will evaluate a dosing schedule for active versus placebo oral naltrexone coadministered with BUP in BUP-dependent individuals prior to first dose of VIVITROL. Eligible subjects will be randomized in a 1:1 ratio to one of 2 treatment groups (naltrexone + BUP or placebo naltrexone [PBO-N] + BUP) for induction onto VIVITROL, stratified according to low (<8 mg/day) versus high (8 mg/day) BUP maintenance dose at the time of initiation of the BUP Lead-in Period. Approximately 92 subjects are planned to be randomized; 46 subjects per group.

The study participation for each subject will last approximately 9 weeks; up to 3 weeks for screening (Days -26 to -6; during which time subjects will remain under the care of their original BUP provider), approximately 2 weeks for the BUP Lead-in Period and the Treatment Period (Days -5 to 7), 4 to 5 days for VIVITROL induction and post-VIVITROL monitoring and a 4-week outpatient follow-up period.

This study includes:

- BUP Lead-in Period: Outpatient Days -5 through -3; residential Days -2 and -1 (option for earlier residential admission at the study clinician's discretion)
- Treatment Period: Transitional dosing with oral naltrexone or PBO-N in conjunction with BUP taper; residential Days 1* to 7

  * Subjects who do not qualify for randomization on Day 1 will receive Day -1 BUP dosing and repeat Day 1 assessments and procedures on the following day, Day 1a.
- VIVITROL Induction and Post-VIVITROL Observation Period:
  - A naloxone challenge and administration of VIVITROL on Day 8* prior to discharge

    * Subjects who do not qualify to receive VIVITROL on Day 8 will receive Day 7 study drug (naltrexone/PBO-N), and complete Day 7 assessments and procedures. Day 8 assessments and procedures will be repeated the following day (Day 8a).
  - Post-VIVITROL outpatient monitoring (Days 9-11)

The design is presented in Figure 1. Each phase is described further below.

Evaluation of withdrawal symptoms will occur throughout the BUP Lead-in Period, the Treatment Period, and the VIVITROL Induction and Post-VIVITROL Observation Period (Days -5 through 11). On Days -2 through 8/8a, AM and PM vital signs, COWS/SOWS, and visual analogue scale (VAS) will be measured (see Section 8.4 for details regarding the timing of these assessments). On the day of discharge (Day 8/8a), PM vital signs, COWS/SOWS and VAS will be measured prior to discharge. In addition to the AM and PM assessments described above, clinical testing sessions to monitor opioid withdrawal effects in response to study drug will occur

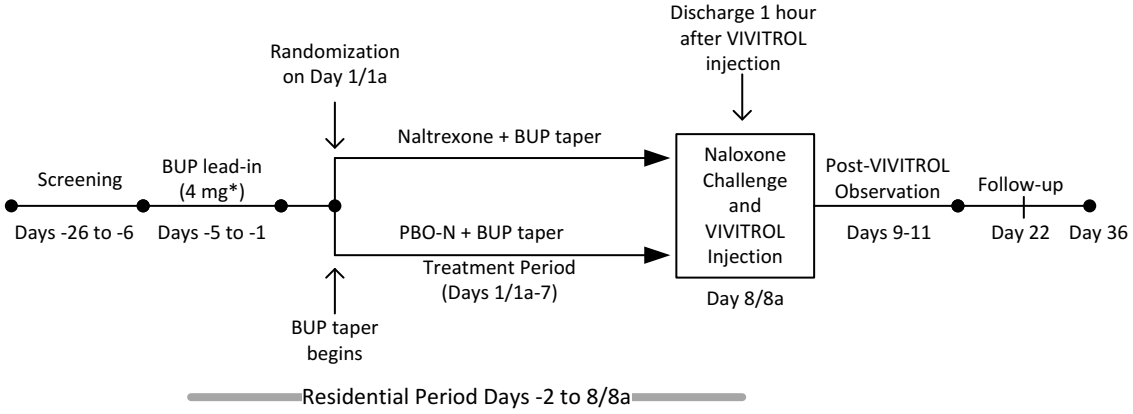
on Days 1 through 7. Also, subjects will receive psychoeducational counseling starting on Day -5 and throughout the Treatment Period.

Up to 2 additional study visits may be conducted (Days 1a and 8a), as needed, for subjects who do not meet criteria for proceeding with procedures on Day 1 or Day 8.

The combined outpatient and residential design of this trial has been selected to ensure tolerability of lower-dose BUP prior to introduction of the treatment regimen, and to afford the most accurate measurement possible of opioid withdrawal during the transition from BUP maintenance to first dose of VIVITROL. Multiple daily observations of opioid withdrawal will be recorded in an environment free from access to nonstudy opioids, thus enabling a more direct comparison of the efficacy of a dosing schedule for active versus placebo oral naltrexone coadministered with BUP to transition BUP-dependent individuals to first dose of VIVITROL. Moreover, this study is the first of its size to examine the transition from opioid agonist to antagonist therapy in this subject population, necessitating careful safety monitoring. Conducting the Treatment Period in a controlled residential environment will ensure that safety and tolerability are carefully monitored. This study will assess the safety, tolerability and efficacy of this procedure for use in a residential or outpatient setting for patients seeking to discontinue BUP and transition to treatment with VIVITROL.

See Section 8.4 for more information on withdrawal assessments and clinical testing sessions, including a timetable for testing sessions in Figure 2. In addition, the Hamilton Rating Scale for Depression (HAM-D) and cognitive assessments will be conducted at screening and on Days -1, 22 and 36.

Figure 1: Study Design Schematic



*Subjects maintained on <4 mg at Day -5 will continue on their current dose until the Treatment Period taper calls for further decrease to establish a consistent daily dose prior to transitional dosing with naltrexone (see Section 8.2.1).

8.2. Buprenorphine Lead-in and Treatment Periods

8.2.1. Buprenorphine Lead-in Period

Following a screening period of up to 21 days, all subjects meeting eligibility criteria will begin a 5-day lead-in period consisting of 3 daily outpatient visits (Days -5 to -3), where subjects will report to the research clinic daily to undergo withdrawal assessments and to receive a dose of

BUP under supervised conditions, then admission to the residential unit on Day -2 in order to ensure tolerability of the BUP maintenance dose in a supervised setting. Subjects may be admitted for residential stay earlier if it is the clinical judgment of the investigator that residential care is needed for management of opioid withdrawal symptoms. In the event that a subject is admitted for the residential stay early (on Days -5, -4, or -3), AM and PM vital signs, COWS/SOWS, and VAS will also be measured. Ancillary medications will not be provided during the outpatient visits (Days -5 to -3), unless needed for treatment or prophylaxis of a documented AE. In the event that a subject is admitted for the residential stay early (on Days -5, -4, or -3), the ancillary medication regimen, which begins on Day -2 (see Section 8.9.2), will begin as soon as the subject becomes residential. To ensure that all subjects initially stabilize on a dose of ≤4 mg BUP daily, and given that such doses are lower than those which afford full μ-opioid receptor occupancy, up to 4 mg BUP will be administered sublingually once daily for 5 days to establish a consistent daily dose prior to transitional dosing with naltrexone. Subjects entering the BUP Lead-in Period at doses of BUP >4 mg/day will have the option, at the discretion of the study physician, to receive an additional take-home dose of BUP 2 mg on Day -5 only. Subjects maintained on ≤4 mg at Day -5 will continue on their current dose until the Treatment Period taper calls for further decrease. Urine toxicology screens will be collected daily during this period. Subjects may miss a single day during the 3-day outpatient BUP Lead-in Period (Days -5 to -3).

8.2.2. Treatment Period

Following 5 days of stabilization on ≤4 mg BUP, on the morning of Day 1 of the Treatment Period, subjects will undergo an assessment of withdrawal symptoms (the eligibility COWS score). Randomization will occur prior to study drug dosing on Day 1. Eligible subjects will demonstrate ability to tolerate the lead-in BUP dose based upon exhibiting minimal/mild opioid withdrawal symptoms (as confirmed by COWS score ≤12) on Day 1. Subjects who do not qualify for randomization on Day 1 will receive Day -1 BUP dosing and complete the remaining Day -1 assessments and procedures. These subjects will then repeat Day 1 assessments and procedures on the following day, Day 1a.

The Treatment Period will consist of tapering doses of BUP (on Days 1/1a-3) in conjunction with ascending doses of oral naltrexone or PBO-N (Days 1/1a-7); see Table 3.

Table 3: ALK6428-A302 Dosing Regimen

Study Day	Group 1 Naltrexone + BUP			Group 2 Placebo-NTX + BUP		
	1st Dose NTX	2nd Dose NTX[a]	BUP[b,c]	1st Dose NTX	2nd Dose NTX[a]	BUP[b,c]
Day -5[d]	N/A	N/A	4 mg	N/A	N/A	4 mg
Day -4	N/A	N/A	4 mg	N/A	N/A	4 mg
Day -3	N/A	N/A	4 mg	N/A	N/A	4 mg
Day -2	N/A	N/A	4 mg	N/A	N/A	4 mg
Day -1	N/A	N/A	4 mg	N/A	N/A	4 mg
Day 1	0.25 mg	0.25 mg	4 mg	PBO-N	PBO-N	4 mg

Table 3: ALK6428-A302 Dosing Regimen (Continued)

Study Day	Group 1 Naltrexone + BUP			Group 2 Placebo-NTX + BUP		
	1st Dose NTX	2nd Dose NTX[a]	BUP[b,c]	1st Dose NTX	2nd Dose NTX[a]	BUP[b,c]
Day 1a	0.25 mg	0.25 mg	4 mg	PBO-N	PBO-N	4 mg
Day 2	0.25 mg	0.25 mg	2 mg	PBO-N	PBO-N	2 mg
Day 3	0.5 mg	0.5 mg	2 mg	PBO-N	PBO-N	2 mg
Day 4	1.5 mg	1.5 mg	N/A	PBO-N	PBO-N	N/A
Day 5	3 mg	3 mg	N/A	PBO-N	PBO-N	N/A
Day 6	7.5 mg	7.5 mg	N/A	PBO-N	PBO-N	N/A
Day 7	15 mg	15 mg	N/A	PBO-N	PBO-N	N/A
Day 8	Naloxone 3.0 mg (1.5 mg + 1.5 mg) then VIVITROL			Naloxone 3.0 mg (1.5 mg + 1.5 mg) then VIVITROL		
Day 8a[e]	Naloxone 3.0 mg (1.5 mg + 1.5 mg) then VIVITROL			Naloxone 3.0 mg (1.5 mg + 1.5 mg) then VIVITROL		

N/A=not applicable; BUP=buprenorphine; NTX=naltrexone; PBO-N=placebo naltrexone

[a] The second dose of naltrexone/PBO-N will be administered at least 60 minutes after the first dose of naltrexone/PBO-N, following a clinical evaluation of tolerability (based upon withdrawal symptoms).

[b] On days when subjects receive both BUP and naltrexone/PBO-N, BUP will be given sublingually immediately following the second dose of oral naltrexone/PBO-N. If a subject does not qualify for the second dose of naltrexone/PBO-N, the subject will still receive the BUP dose for that day and will be monitored in the clinic for 60 minutes following the BUP dose.

[c] Subjects maintained on <4 mg at study entry will continue on their current dose until the treatment period taper calls for further decrease to establish a consistent daily dose prior to transitional dosing with naltrexone.

[d] Subjects entering the BUP Lead-in Period at doses of BUP >4 mg/day will have the option, at the discretion of the study physician, to receive an additional take-home dose of BUP 2 mg on Day -5 only.

[e] If a subject has a positive naloxone challenge on Day 8, he/she will not receive the VIVITROL injection, but will receive Day 7 study drug (naltrexone/PBO-N), and complete Day 7 assessments and procedures. He/she will be offered the opportunity to remain in the residential unit overnight and may repeat the naloxone challenge the following day (Day 8a) to qualify for VIVITROL administration.

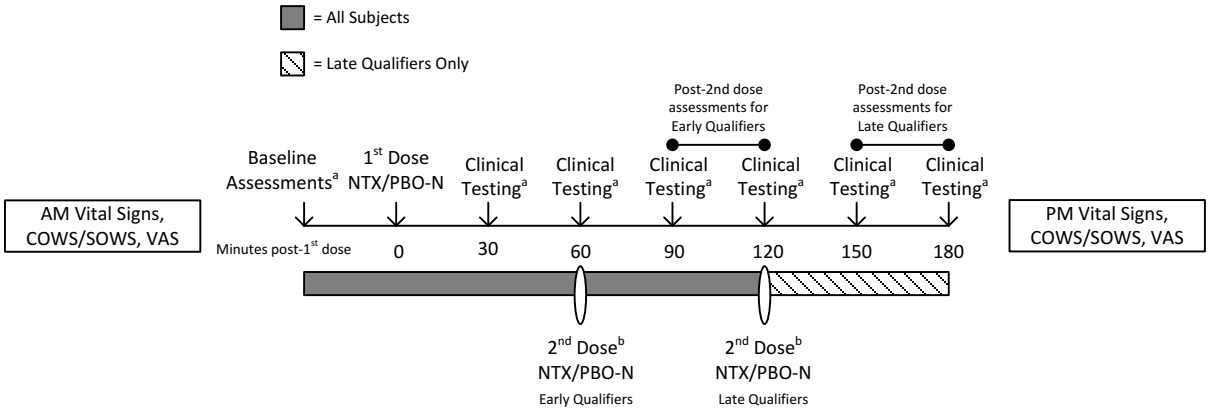
The total daily naltrexone or PBO-N allocation will be split over 2 separate doses administered at least 60 minutes apart. Administration of the second naltrexone or PBO-N dose will depend upon how well the first was tolerated.

On Days 1/1a through 7, subjects will undergo a baseline COWS and SOWS assessment prior to the first dose of naltrexone or PBO-N (see Figure 2). On Day 1/1a, the eligibility COWS score may serve as the predose COWS score, if conducted within 60 minutes prior to dosing. At 30 and 60 minutes postdose, the COWS and SOWS will be re-administered. If withdrawal symptoms are stable (ie, increase of ≤5 points in COWS score from predose COWS) at the 60-minute assessment, the second dose of oral naltrexone or PBO-N will be administered. For these early qualifying subjects, the next COWS/SOWS assessments at 90 and 120 minutes post-first dose will constitute their post-second dose assessments.

Subjects who did not qualify for the second dose of naltrexone or PBO-N at 60 minutes will also receive the 90- and 120-minute COWS/SOWS assessments (see Figure 2), and if their withdrawal symptoms have stabilized sufficiently by 120 minutes post-first dose (ie, increase of

≤5 points in COWS score from predose COWS), they will receive the second dose of oral naltrexone or PBO-N at this time. These later qualifying subjects will undergo 2 additional COWS/SOWS assessments at 150 and 180 minutes post-first dose (30 and 60 minutes post-second dose) to monitor withdrawal status following the second dose of naltrexone or PBO-N. Refer to Section 8.2.3 for instructions on how to proceed should withdrawal symptoms not stabilize by 120 minutes.

Figure 2: Schematic of Daily Residential Withdrawal Assessments, Days 1/1a to 7



[a]Clinical testing sessions will include the following assessments: vital signs (body temperature, respiratory rate, heart rate, systolic and diastolic blood pressure), oxygen saturation, pupillometry, SOWS, COWS, Opioid Craving VAS. A window of +30 minutes is allowed for these assessments.
[b]Subjects whose COWS score is increased ≤5 points above the baseline COWS qualify for the second dose of NTX or PBO-N immediately followed by BUP (on BUP dosing days). Subjects who do not qualify for the second dose by the 120-minute timepoint will not receive a second dose of NTX/PBO-N, but will receive the normal dose of BUP (on BUP dosing days).

Buprenorphine will be administered sublingually immediately following the second oral naltrexone or PBO-N dose on Days 1/1a through 3. If a subject does not qualify for the second dose of naltrexone or PBO-N, he/she will still receive the BUP dose for that day (see Section 8.2.3). Subjects will remain under clinical observation for a minimum of 60 minutes after the BUP dose to assess tolerability of withdrawal symptoms.

8.2.3. Poorly Tolerated Doses

If withdrawal symptoms increase substantially after the initial dose of naltrexone or PBO-N (ie, COWS score increased >5 points from the predose COWS) and do not recede during subsequent COWS/SOWS testing (up to 120 minutes postdose), the subject will not receive the second dose of naltrexone or PBO-N, but may receive the scheduled dose of BUP, as well as ancillary medications. Following BUP administration, the subject will be observed for 60 minutes in the clinical setting. In addition to the standing regimen of ancillary medications (see Section 8.9.2), subjects may be administered additional doses of ancillary medications, as needed to alleviate any marked withdrawal symptoms (ie, total COWS score >12) not alleviated by BUP. The subject will continue all clinical testing sessions and the dosing scheduled for the following day.

8.3. Day 8/8a Naloxone Challenge and VIVITROL Injection

8.3.1. Naloxone Challenge

Prior to the start of the naloxone challenge, COWS/SOWS assessments will be administered. Subjects who are no longer exhibiting significant signs of withdrawal as demonstrated by COWS total score ≤12 on Day 8/8a will undergo a 2-part naloxone challenge as follows:

Part 1:

- Administer 1.5 mg* of naloxone intramuscularly in the subject's arm (nondominant arm preferred for first injection)

  * Note: Each naloxone injection consists of 1.5 mg. Doses of naloxone sufficient to precipitate opioid withdrawal in the presence of short-acting opioids may not suffice to displace BUP from the μ-opioid receptor (Gal 1989).

- Administer COWS and SOWS at 10 and 20 minutes post-naloxone injection. Vital signs will be measured and the subject will remain under observation following the naloxone injection to monitor for safety
  - At each timepoint (10 and 20 minutes) the COWS score must be no more than 2 points greater than the pre-naloxone baseline COWS score for subjects to qualify for Part 2.
  - If either the 10- or 20-minute COWS score increases by >2 points from the pre-naloxone COWS, then the challenge is considered to be positive (see Section 8.3.3.1 for instructions on how to proceed following a positive naloxone challenge). A positive challenge is indicative of a significant increase in withdrawal symptoms and physical dependence on opioids.

Part 2:

- Administer second naloxone injection (1.5 mg [see Part 1 above regarding dose] naloxone in opposite arm to that used for first injection)
- Administer COWS and SOWS at 10 and 20 minutes post-naloxone injection. Vital signs will be measured and the subject will remain under observation following the naloxone injection to monitor for safety
  - At each timepoint (10 and 20 minutes) the COWS score must be no more than 2 points greater than the immediately previous Part 1 COWS score for subjects to qualify for VIVITROL injection
  - If either the 10- or 20-minute COWS score in Part 2 increases by >2 points from the immediately previous Part 1 COWS score, then the challenge is considered to be positive. See Section 8.3.3.1 for how to proceed following a positive naloxone challenge.

    Eligibility for VIVITROL administration on Day 8/8a will consist of the following: Part 1 post-naloxone COWS scores increase by ≤2 points from pre-naloxone scores and Part 2 post-naloxone COWS scores increase by ≤2 points from the immediately previous Part 1 score, with a total allowable increase of

≤4 points in COWS total score for Parts 1 and 2 of the challenge combined. Subjects must have a total COWS score ≤16 following the naloxone challenge to qualify for VIVITROL administration. Subjects with a positive naloxone challenge on Day 8 will have the opportunity to retry the challenge on the following day (Day 8a; see Section 8.3.3.1)

8.3.2. VIVITROL Injection

If the naloxone challenge is negative, a single intramuscular (gluteal) injection of VIVITROL 380 mg will be administered following the naloxone challenge on Day 8/8a. Subjects will remain on-site for 1 hour for safety observation following VIVITROL administration and then may be discharged home, following PM withdrawal assessments. They will be asked to return for outpatient visits on the 3 days following VIVITROL injection (Days 9-11).

8.3.3. Subjects Who Do Not Transition to VIVITROL

Due to loss of opioid tolerance and a heightened risk for overdose in subjects who have transitioned from BUP but have not received VIVITROL (due to subject withdrawal of consent or a positive naloxone challenge), it is important that subjects be reinstated on BUP/Nx maintenance therapy and discharged to their treatment provider to continue BUP maintenance and discuss future treatment options.

8.3.3.1. Treatment Options for Subjects with a Positive Naloxone Challenge

8.3.3.1.1. Day 8

Subjects with a positive naloxone challenge on Day 8 will not receive the VIVITROL injection that day. In such cases, these subjects will receive Day 7 study drug (naltrexone/PBO-N), and complete Day 7 assessments and procedures (per Figure 2). Pre- and postdose COWS will be assessed for clinical safety purposes only. Day 8 assessments and procedures will be repeated the following day (Day 8a).

For subjects who do not wish to receive a naloxone challenge on Day 8a, the study staff will notify the subject's BUP provider prior to discharge, to inform him/her of the treatment and medications the subject has received during the course of the study, and of the need for a follow-up appointment. Such subjects will be restarted on BUP/Nx while on the residential unit at a dose deemed clinically sufficient. Depending upon how many days of blinded treatment medication they have received, the investigator may decide that, for safety reasons, the subject should remain in the residential unit for up to 48 hours. Upon discharge he/she will be provided up to 3 days of BUP maintenance. The subject may choose to discuss other future treatment options with his/her BUP provider.

8.3.3.1.2. Day 8a

Subjects with a positive naloxone challenge on Day 8a will not receive the VIVITROL injection that day. In such cases, the study staff will follow the discharge procedures described in Section 8.3.3.1.1 above.

8.3.3.2. Treatment Options for Subjects Who Discontinue Prior to Receiving VIVITROL

For subjects who discontinue from the study during the course of the residential period, the procedures described in Section 8.3.3.1.2 will be followed.

8.3.4. Referrals to Post-Study VIVITROL Provider

Subjects who have received VIVITROL will return to their previous BUP provider to receive subsequent VIVITROL treatment, unless the subject has chosen to transfer to a new treatment provider. Study staff will work with subjects to identify local VIVITROL treatment providers, as necessary. Subjects will be asked to sign consent for release of clinical record, not to include study data, to contact the post-study VIVITROL provider for purposes of follow-up medical care.

8.4. Withdrawal Assessments Throughout the Residential Period

Every morning (AM) and every evening (PM) during the residential period (Days -2 to 8/8a) subjects will undergo a basic withdrawal evaluation consisting of COWS, SOWS, VAS, and vital signs (Figure 2). The AM assessments should be conducted first thing in the morning and ≥60 minutes prior to the baseline assessments. On Day 8/8a, the COWS/SOWS conducted as part of the AM assessments can serve as the pre-naloxone challenge COWS/SOWS if they are administered within an hour (≤60 minutes) prior to the initial administration of naloxone in Part 1 of the naloxone challenge. The PM assessments should be conducted in the evening. In the event that they cannot be conducted in the evening, the earliest they can be completed is at 60 minutes after the 120-minute post-first NTX/PBO-N dose for early qualifiers, and at 60 minutes after the 180-minute post-first NTX/PBO-N dose for late qualifiers. The 60-minute post-VIVITROL injection assessments on Day 8/8a can serve as the PM assessments for those days.

In the event that a subject is admitted for the residential stay early (on Days -5, -4 or -3), standard AM and PM assessments should be conducted. For subjects who remain on the residential unit for clinical stabilization on BUP, these study assessments are not required.

On Days 1/1a to 7, subjects will undergo daily clinical testing to measure opioid withdrawal effects in response to study drug dosing. These clinical testing sessions will include the following assessments (see Section 8.8 for more details on individual assessments):

- Vital signs (body temperature, respiration rate, heart rate, systolic and diastolic blood pressure)
- Oxygen saturation
- Pupillometry
- COWS
- SOWS
- VAS

A timetable for clinical testing sessions is provided in Figure 2. On Days 1/1a to 7, clinical testing sessions will begin approximately 15 minutes prior to the first dose of naltrexone or

PBO-N and will last at least 120 minutes following the first dose (60 minutes following the second dose). Clinical testing may potentially last 180 minutes for late qualifying subjects who receive the second naltrexone or PBO-N dose at the 120-minute timepoint (see Section 8.2.2 for more information regarding early and late qualification). A window of +30 minutes is allowed for these assessments.

On Day 8/8a, VAS, COWS/SOWS, vital signs, and pupillometry will be collected pre-VIVITROL injection, and at 30 and 60 minutes post-VIVITROL injection. The final COWS/SOWS assessments of the naloxone challenge will also represent the pre-VIVITROL COWS/SOWS scores. Subjects will be discharged following the 60-minute post-VIVITROL assessments.

8.5. Follow-up Period

On Study Days 22 (±3 days) and 36 (±3 days), subjects who have completed the Treatment Period and the VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11) will return to the research center for 2 outpatient follow-up visits that will occur 2 and 4 weeks after the naloxone challenge/VIVITROL injection.

8.6. Minimizing Risks

Participants are fully informed by investigators of the potential side effects of the drugs and the risks of the procedures. In addition participants are advised about the risk of taking an opioid (BUP) in conjunction with benzodiazepines, other CNS depressant medicines or alcohol. Participants are monitored for oxygen saturation and vital signs by trained medical staff during clinical testing sessions. Emergency medical equipment is available in the testing clinic and the clinic is located in either a hospital where a full medical emergency back-up team is constantly available; or a medical research facility with appropriate emergency response procedures. Additionally, guidelines have been developed for opioid administration such that oxygen saturation dictates whether supplemental oxygen will be administered. Naloxone is available during all laboratory sessions in the event of serious respiratory depression. It is anticipated, however, that careful participant selection, dose selection and participant monitoring will eliminate the need for such emergency care.

Enrolling subjects who are currently under the care of waivered physicians with the ability to prescribe BUP ensures that all subjects will have access to an addiction treatment provider at the completion of the study, or upon termination of participation in the trial. While it is anticipated that many subjects will transition to VIVITROL during the study, those who are not successful at induction will be advised to return to BUP maintenance under the care of their prior BUP treatment provider, with whom they can discuss additional treatment options.

See Section 8.3.3.1 for instructions on how to proceed with subjects who are discharged without receiving VIVITROL. If not returned to a stable daily dose of BUP/Nx, these subjects will be at greater risk for relapsing to illicit or nonmedical use of opioids. Relapse also carries the risk of overdose.

Subjects who have transitioned to VIVITROL and wish to transition to a different treatment provider will be offered referrals to local providers who prescribe medication-assisted treatment, including VIVITROL and BUP.

8.7. Schedule of Visits and Assessments

The schedule of visits and assessments is shown in Table 4.

For a missed visit, the site should attempt to contact the subject to reschedule.

Premature discontinuation procedures are provided in Section 7.3.

Table 4: Schedule of Visits and Assessments

	Screening Period	BUP Lead-in Period			Treatment Period										Naloxone Challenge, VIVITROL, and post-VIVITROL observation					Follow-Up	
Study Visit	**1**	**2**	**3**	**4**	**5**												**6**	**7**	**8**	**9**	**10**
Study Day	**-26 to -6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**1a[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**8a[b]**	**9/ET**	**10**	**11**	**22 (±3 days)**	**36 (±3 days)**
Informed Consent	X																				
Eligibility Criteria Review	X																				
Demographics and Medical History	X																				
MINI	X																				
MMSE[c]	X						X	X	X	X	X	X	X	X							
MOTYB[c]							X	X	X	X	X	X	X	X							
SMAST	X	X			X															X	X
Pregnancy Test[d]	X	X					X	X							X	X					X
Physical Examination[e]	X														X	X					
Height	X																				
Weight	X																				
ECG	X																				X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry, Hematology and Urinalysis Samples	X														X						X
Breath Alcohol Test	X	X			X																

Table 4: Schedule of Visits and Assessments (Continued)

	Screening Period	BUP Lead-in Period			Treatment Period										Naloxone Challenge, VIVITROL, and post-VIVITROL observation					Follow-Up	
Study Visit	**1**	**2**	**3**	**4**	**5**												**6**	**7**	**8**	**9**	**10**
Study Day	**-26 to -6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**1a[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**8a[b]**	**9/ET**	**10**	**11**	**22 (±3 days)**	**36 (±3 days)**
Drug Screen[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X
Residential Admission					X																
Residential Discharge															X	X					
Randomization[h]							X	X													
Administration of NTX/PBO-N							X[i]	X	X	X	X	X	X	X	X[i]						
Administration of BUP		X	X	X	X	X	X	X	X	X											
Ancillary Medications[j]					X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]	X[k]		
Naloxone Challenge															X	X					
VIVITROL Injection															X	X					
QSUI	X	X	X	X													X	X	X	X	X
COWS[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X[m]	X	X	X	X	X
SOWS[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X[m]	X	X	X	X	X
Desire for Opioids VAS[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pupillometry[n]							X	X	X	X	X	X	X	X	X	X					

Table 4: Schedule of Visits and Assessments (Continued)

	Screening Period	BUP Lead-in Period			Treatment Period										Naloxone Challenge, VIVITROL, and post-VIVITROL observation					Follow-Up	
Study Visit	**1**	**2**	**3**	**4**	**5**												**6**	**7**	**8**	**9**	**10**
Study Day	**-26 to -6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**1a[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**8a[b]**	**9/ET**	**10**	**11**	**22 (±3 days)**	**36 (±3 days)**
PGART															X[o]	X[o]	X[p]		X		X
C-SSRS[q]	X	X					X	X		X							X		X	X	X
Psychoeducational Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X
HAM-D[r]	X[s]					X														X	X
Cognitive Assessments[t]	X[s]					X														X	X
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; ET=early termination; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; HAM-D=Hamilton Rating Scale for Depression; MINI=Mini-International Neuropsychiatric Interview; MMSE=Mini-Mental Status Examination; MOTYB=Months of the Year Backward; NTX=naltrexone; PBO-N=placebo naltrexone; PGART=Patient Global Assessment of Response to Therapy; QSUI=Quantitative Substance Use Inventory; SMAST= Short Michigan Alcohol Screening Test; SOWS=Subjective Opiate Withdrawal Scale; VAS=Visual Analogue Scale

[a] Subjects who do not qualify for randomization on Day 1 will receive Day -1 BUP dosing and repeat Day 1 assessments and procedures on the following day, (Day 1a).

[b] Subjects who do not qualify to receive VIVITROL on Day 8 will receive Day 7 study drug (naltrexone/PBO-N), and complete Day 7 assessments and procedures. Pre- and postdose COWS will be assessed for clinical safety purposes only. Day 8 assessments and procedures will be repeated the following day (Day 8a).

[c] Full MMSE will be conducted at screening. The MMSE orientation questions and MOTYB will be performed 60 (-5/+15) minutes following the second dose of oral naltrexone/PBO-N or at end of testing session for subjects not receiving second dose.

[d] For female subjects only. Urine pregnancy tests will be conducted at all specified timepoints; in addition, serum pregnancy tests will be conducted at Screening and Day 1/1a. Urine pregnancy tests to be performed prior to randomization on Day 1/1a and prior to naloxone challenge on Day 8/8a.

[e] Full physical examination at screening and symptom-driven examinations at subsequent timepoints.
[f] In addition to the study assessments conducted during the clinical testing sessions, vital signs will be measured each morning and evening throughout the residential period (Days -2 to 8/8a and any additional residential days, in the case of earlier admission or later discharge). Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be measured after the subject has been in a seated position for at least 5 minutes. In addition to standard vital sign measurements, clinical testing sessions on Days 1/1a to 7 will include oxygen saturation and pupillometry measurements to assess withdrawal effects in response to drug dosing. Measurements will be collected pre- and postdose as indicated in Figure 2. Details regarding the timing of these assessments are provided in Section 8.4.
[g] A urine drug screen will be performed at all specified timepoints. The urine drug screen should be performed in the morning. On Days 1/1a to 7, it should be performed prior to the clinical testing sessions.
[h] Eligibility will be confirmed prior to randomization and administration of the first dose of NTX/PBO-N.
[i] Subjects not qualifying for randomization on Day 1 will receive the Day -1 BUP dose and will not receive NTX/PBO-N. Subjects not qualifying for VIVITROL on Day 8 will receive the Day 7 NTX/PBO-N dose, along with the COWS conducted for clinical safety purposes only.
[j] Standing ancillary medication regimen begins on Day -2. In the event that a subject is admitted for the residential stay early (on Days -5, -4, or -3), the ancillary medication regimen will begin as soon as the subject becomes residential. Also, if needed for AE treatment or prophylaxis, ancillary medications may be initiated at the clinician's discretion on or after Day -5
[k] For subjects receiving VIVITROL on Day 8/8a, ancillary medications will be reduced as indicated in Table 6.
[l] COWS, SOWS and VAS to be recorded each morning (AM) and evening (PM) throughout the residential period (Days -2 to 8/8a) and any additional residential days, in the case of earlier admission or later discharge. On Days 1/1a to 7 the COWS, SOWS and VAS will also be administered as part of clinical testing sessions to measure withdrawal effects in response to study drug dosing. Details regarding the timing of these assessments are provided in Section 8.4.
[m] On Day 8/8a, additional COWS and SOWS assessments will occur with the naloxone challenge, separate from the clinical testing sessions (pre-naloxone and 10 and 20 minutes following each naloxone injection; see Section 8.3.1 for details).
[n] Pupillometry to be performed during clinical testing sessions to evaluate withdrawal in response to study drug dosing on Days 1/1a to 7, as well as pre-VIVITROL injection, and at 30 and 60 minutes post-VIVITROL injection on Day 8/8a. A timetable showing when pupillometry occurs in relation to study drug dosing can be found in Figure 2.
[o] The PGART will be administered prior to VIVITROL injection on Day 8/8a.
[p] For ET visit only.
[q] The "Baseline/Screening" version to be used at screening. The "Since Last Visit" version to be used at all subsequent visits.
[r] The HAM-D should be administered immediately prior to the cognitive assessments.
[s] Initial HAM-D and cognitive assessments should be conducted as early as possible during the screening period.
[t] The cognitive assessments that will be conducted are described in detail in Section 8.8.11.12. Cognitive assessments at screening and during the follow-up period should be conducted after the completion of all other assessments during the visit. On Day -1, cognitive assessments may be conducted at any time after the morning vital sign and withdrawal measurements and prior to the evening vital sign and withdrawal measurements. Caffeine and nicotine use are prohibited within 30 minutes prior to the start of cognitive assessments.

8.8. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedule of assessments is provided in Table 4.

8.8.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the principal investigator or designated study personnel as outlined in Section 16.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential subject.

8.8.2. Eligibility Review

An eligibility review will be conducted by the investigator at the visits specified in Table 4 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

8.8.3. Demographics and Medical History

Subject's demographic data and medical history will be reviewed and documented at the timepoint specified in Table 4.

8.8.4. Concomitant Medication Review

All medications (prescription and nonprescription, including vitamins and herbal supplements) taken by a given subject within 30 days of screening through follow-up will be recorded.

At each study visit (see Table 4), the investigator or designee will record the following data on all medications used by the subject: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

8.8.5. Vital Signs and Oxygen Saturation

Vital signs (ie, body temperature, respiratory rate, heart rate and blood pressure) will be assessed at the timepoints specified in Table 4. Respiratory rate, heart rate and blood pressure will be measured after the subject has been resting in a seated position for at least 5 minutes.

Heart rate, blood pressure (systolic and diastolic) and respiration rate will be measured and recorded pre- and postdose according to the timetable provided in Figure 2. In addition to vital signs, arterial oxygen saturation will be measured according to the same timetable using a soft sensor placed over the fingertip on the nondominant hand.

8.8.6. Pupillometry

Pupillometry will be conducted in a consistent level of ambient light during clinical testing sessions at the timepoints indicated in Table 4 according to the timetable indicated in Figure 2. Pupil diameter will be measured before and after drug administration using a digital pupillometer. Mean peak (ie, maximum) pupil diameter (which will be noted as "Mean" on the printout) will be recorded manually and then entered into the eCRF. Output will be saved with the appropriate source documents for each subject.

8.8.7. Physical Examination

A physical examination will be performed at the timepoints specified in Table 4, a full physical exam at screening and symptom-driven exams at subsequent timepoints.

8.8.8. Body Height and Weight

Body height and weight will be measured at screening only.

8.8.9. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at the timepoints specified in Table 4.

8.8.10. Behavioral Therapy: Psychoeducational Counseling

Subjects who enter the study will be asked to participate in psychoeducational counseling at the timepoints specified in Table 4. Counseling will be conducted by qualified study staff that will review common withdrawal symptoms, and instruct subjects on correct medication usage and the importance of adherence to study and ancillary medications.

Subjects who were participating in counseling sessions prior to study entry will be encouraged to continue their program upon discharge from the inpatient stay. Subjects will also be provided information about local resources for addiction support upon exit from the study.

8.8.11. Structured Interviews and Questionnaires

8.8.11.1. Mini-International Neuropsychiatric Interview

The MINI will be administered at screening (Table 4). The MINI is a short, clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes. The MINI has been validated against the much longer Structured Clinical Interview for DSM diagnoses. A sample of the MINI can be found in Appendix A.

8.8.11.2. Mini-Mental Status Examination

The MMSE is an 11-item, 30-point, clinician-administered questionnaire used to assess global cognitive impairment (Faust and Fogel 1989). A score ≤23 is indicative of cognitive impairment consistent with possible delirium or dementia. The full MMSE is administered at screening. On treatment days (Days 1/1a-7; Table 4), only orientation questions (MMSE items 1-2) will be asked. A decrease in score of 2 points total in the orientation questions is indicative of a change in mental status and requires a clinical assessment, as described below, prior to continuing protocol procedures for that day.

The study staff may repeat the administration of the MMSE orientation questions if performance was deemed to be affected by fatigue or a medication effect. If a decrease of ≥2 points from baseline is confirmed on the MMSE, the study physician will conduct a clinical interview with the subject to confirm that the subject is alert, oriented, and consents to continuing the study procedures. If these conditions are not met, the subject will be observed on site and reassessed after 30 minutes. If orientation remains altered, the subject will be referred for medical evaluation. If the medical evaluation results in hospitalization, this would constitute an SAE.

8.8.11.3. Months of the Year Backward

The Months of the Year Backward (MOTYB) is a brief assessment of verbal working memory, which is also used to screen for delirium (Meagher et al, 2015). Subjects will be instructed to recite the months of the year forward, and then backward. Subjects will receive a score of 0 to 2. Scores ≤1 indicate the absence of delirium.

This assessment may be repeated if fatigue or poor effort is deemed to have interfered with the subject's performance. An increase in MOTYB score will warrant assessment by the study physician. As noted above (Section 8.8.11.2), a subject found to have altered sensorium will be referred for medical evaluation, and if hospitalized, this event would constitute an SAE.

Subjects will complete the MOTYB on Days 1/1a through 7, as indicated in Table 4.

8.8.11.4. Columbia Suicide Severity and Rating Scale

The C-SSRS is a questionnaire administered by a qualified clinician that assesses suicidal ideation and behavior (Posner et al, 2011). The "Baseline/Screening" version of the scale will be administered at the screening visit. The "Since Last Visit" version will be administered at all other timepoints specified in Table 4. Samples of the C-SSRS can be found in Appendix B.

8.8.11.5. Clinical Opiate Withdrawal Scale

The COWS is a questionnaire designed to measure 11 common opioid withdrawal signs or symptoms (Wesson and Ling 2003). The summed score provides information about the level of physical dependence on opioids. The COWS will be administered by research staff at the timepoints specified in Table 4. In addition to morning and evening assessments throughout the residential period, the COWS will be administered during clinical testing sessions (see Section 8.4) according to the timetable provided in Figure 2. A sample of the COWS can be found in Appendix C. When possible, the same person should complete the COWS each time.

8.8.11.6. Subjective Opiate Withdrawal Scale

The SOWS is a 16-item self-report questionnaire designed to measure the severity of opioid withdrawal symptoms. The subject rates the intensity of symptoms using a 5-point scale; with 0 representing "not at all" and 5 representing "extremely." The SOWS will be self-administered at the timepoints specified in Table 4. In addition to morning and evening assessments throughout the residential period, the SOWS will be self-administered during clinical testing sessions (see Section 8.4) according to the timetable provided in Figure 2. A sample of the SOWS can be found in Appendix D.

8.8.11.7. Desire for Opioids Visual Analogue Scale

The desire for opioids will be measured using a 100-mm, horizontal VAS, with 0 anchored on the left representing "no desire for opioids" and 100 anchored on the right representing "strongest imaginable desire for opioids." Subjects will place a vertical line on the scale to indicate their desire for opioids at that particular time. The VAS will be self-administered at the timepoints specified in Table 4. In addition to morning and evening assessments throughout the residential period, the VAS will be self-administered during clinical testing sessions (see

Section 8.4) according to the timetable provided in Figure 2. A sample can be found in Appendix E.

8.8.11.8. Short Michigan Alcohol Screening Test

The SMAST is a 13-item self-report instrument designed to measure problems experienced as a result of drinking alcohol. The responses are coded as "yes/no." All "Yes" responses indicate problems associated with drinking except for items #1, #4 and #5; for these items, "No" responses indicate problems associated with drinking. As a research tool, the SMAST has >90 percent sensitivity for identifying alcohol use disorder. The SMAST will be self-administered at the timepoints specified in Table 4. A sample of the SMAST can be found in Appendix F.

8.8.11.9. Quantitative Substance Use Inventory

The Quantitative Substance Use Inventory (QSUI) is a 29-item questionnaire designed to quantify drug use in a specified period, including classes of drugs, particular substances, as well as the route of administration. Subjects will complete the QSUI at the timepoints indicated in Table 4. A sample of the QSUI can be found in Appendix G.

8.8.11.10. Patient Global Assessment of Response to Therapy

Treatment satisfaction will be assessed using the Patient Global Assessment of Response to Therapy (PGART). The PGART consists of one item: "How would you rate your response to the medication that you received during the study?" It is measured on a 5-point Likert scale (0=poor, 4=excellent). The PGART will be self-administered at the timepoints specified in Table 4. A sample of the PGART can be found in Appendix H.

8.8.11.11. Hamilton Rating Scale for Depression

The 17-item HAM-D is a clinician-administered depression scale designed to be sensitive to treatment effects (Hamilton 1960). The HAM-D will be administered at the timepoints specified in Table 4. The Structured Interview Guide for the HAM-D (SIGH-D) will be used for administration. A sample of the SIGH-D can be found in Appendix I.

8.8.11.12. Cognitive Assessments

The Brief Assessments of Cognition (BAC) Symbol Coding test, Controlled Oral Word Association (COWA) task, Wechsler Memory Scale-III Spatial Span (WMS-III SS) test, Continuous Performance Test (CPT) and Test of Attentional Performance (TAP) will be administered at the timepoints specified in Table 4.

8.8.11.12.1. Brief Assessments of Cognition Symbol Coding Test

The BAC Symbol Coding test is used to measure cognitive processing speed (Keefe 1999). During this task, subjects are given a list of numbers (numerals 1-9) that are each associated with a unique symbol. Subjects decode a list of 110 symbols as quickly as possible in 90 seconds. The total number of symbols correctly decoded can range from 0 to 110. Total administration time (including instruction and practice items) is 3 minutes. A sample of the BAC Symbol Coding test administrator instructions and respondent form can be found in Appendix J.

8.8.11.12.2. Controlled Oral Word Association Task

The COWA is a verbal fluency task (Benton et al, 1983). Subjects are asked by a rater to spontaneously produce words belonging to a common category or beginning with the same designated letter. Total administration time is 5 minutes. A sample of the COWA task administrator instructions can be found in Appendix K.

8.8.11.12.3. Wechsler Memory Scale-III Spatial Span Test

The WMS-III SS test is a measure of working memory (Wechsler 1997). Subjects are presented with a board containing blue blocks that are randomly arranged. The clinician begins by tapping out a pattern of blocks, beginning with a sequence of 2 blocks and increasing the length of the pattern with subject proficiency (up to a sequence of 9 blocks). During the first part of the test, the subject is tasked with tapping the same pattern as the clinician. During the second part of the test, the subject is tasked with tapping out the reverse pattern of that demonstrated by the clinician. The total score ranges from 0 to 32. Total administration time is 8 minutes. A sample of the WMS-III SS administrator instructions can be found in Appendix L.

8.8.11.12.4. Continuous Performance Test

The CPT is a computer-based task that measures attention and vigilance (Cornblatt et al, 1988). Subjects are asked to attend to digits flashing on the computer screen and to click the mouse when the same string of digits flashes consecutively. There are 3 trials of this subtest; the first containing 2-digit sequences, the second containing 3-digit sequences and the third containing 4-digit sequences. Scoring for this subtest is based on “hits” versus “false alarms” and “randoms,” and the total score is represented by a d-prime quotient ranging from -1.00 to 4.24. Total administration time is 10 minutes. Screenshots of the CPT instructions can be found in Appendix M.

8.8.11.12.5. Test of Attentional Performance

The TAP is a computer-based divided attention task that involves the simultaneous processing of visual and auditory stimuli (Zimmermann and Fimm 2002). For the visual component, a region of the screen displays a varying number of crosses simultaneously. When 4 of the crosses form a square, the subject is required to press the designated key as quickly as possible. For the auditory component, the subject hears a sequence of high and low tones. When the same tone occurs twice in a row, the subject is required to press the designated key as quickly as possible. The subject is required to pay attention to both the crosses and the tones at the same time. Total administration time is 2.5 to 6 minutes. A screenshot of the TAP instructions can be found in Appendix N.

8.8.12. Laboratory Assessments

8.8.12.1. Pregnancy Testing

A serum pregnancy test will be performed for all women at screening and Day 1/1a. A urine pregnancy test will be performed at Day 1/1a, as well as all subsequent timepoints specified in Table 4. Results must be negative for initial study eligibility and continued participation.

8.8.12.2. Urine Drug Screen

A urine drug screen will be performed, via urine dipstick, at the timepoints specified in Table 4. The urine drug screen will test for opioids, illicit substances and other drugs of abuse (eg, opiates, methadone, oxycodone, BUP, cocaine, amphetamine, methamphetamine, tetrahydrocannabinol, benzodiazepines, barbiturates, propoxyphene and phencyclidine).

The urine drug screen may be repeated at the investigator's discretion.

8.8.12.3. Breath Alcohol Test

A breathalyzer test for alcohol will be performed at the timepoints specified in Table 4. Subjects must have a negative breath alcohol test prior to admission to the residential unit (Day -2). The breath alcohol test may be repeated at the investigator's discretion.

8.8.12.4. Clinical Laboratory Assessments

Blood and urine samples will be collected at the timepoints specified in Table 4 for specific hematology, biochemistry and urinalysis assessments listed in Table 5. Samples will be collected in accordance with the site's standard procedures and analyzed by a central laboratory. Laboratory assessments may be repeated at the investigator's discretion.

Table 5: Clinical Laboratory Assessments

Hematology	Chemistry	Urinalysis
Hematocrit	Sodium	Color
Hemoglobin	Potassium	pH
Red blood cell count	Glucose	Specific gravity
White blood cell count and differential[a]	Creatinine	Ketones
Platelets	Total protein	Protein
	Blood urea nitrogen (BUN)	Glucose
	Albumin	Bilirubin
	Total bilirubin	Nitrite
	Alanine aminotransferase (ALT)	Urobilinogen
	Aspartate aminotransferase (AST)	Occult blood
	Lactic dehydrogenase (LDH)	Microscopic examination *only if urinalysis dipstick results are abnormal*
	Gamma-glutamyl transferase (GGT)	
	Alkaline phosphatase (ALK-P)	
	Creatine phosphokinase (CPK)	
	Thyroid stimulating hormone (TSH)[b]	

[a] White blood cell differential count (absolute values) will include basophils, eosinophils, lymphocytes, monocytes and neutrophils.
[b] At screening only.

8.8.13. Randomization

At the timepoint specified in Table 4, subjects will be randomized as outlined in Section 9.4.

8.8.14. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug (naltrexone, PBO-N, BUP, naloxone and VIVITROL) will be administered by clinical study staff at the timepoints specified in Table 4. The clinical study site is responsible for study drug storage, handling and accountability as outlined in Section 10.

8.8.15. Adverse Event Monitoring

AEs will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit (see Table 4). AEs and SAEs are defined in Section 12.1 and 12.2, respectively. Section 12.4 provides guidance on the monitoring and recording requirements for AEs. Section 12.5 provides guidance on the reporting requirements for SAEs.

8.9. Study Requirements and Restrictions

8.9.1. Prohibited Medications and Substances

The medications and substances listed below are prohibited for the specified time periods:

- Methadone is prohibited at least 30 days prior to Day -5 and for the duration of the study
- All opioid agonists (except BUP when administered during applicable study days), including opioid-containing cough medications, are prohibited for the duration of the study
- Naltrexone is prohibited for at least 90 days prior to Day -5 and for the duration of the study (except when administered during applicable study visits)
- On days when cognitive assessments are conducted (see Table 4), caffeine and nicotine (oral, inhaled or smoked) are prohibited within 30 minutes prior to the start of the assessments. A transdermal nicotine patch may remain in place. Throughout the residential period, nicotine replacement therapy is permissible in accordance with prevailing clinical policy of the residential unit.

8.9.2. Ancillary Medications

Subjects will receive ancillary medications on a standing schedule to treat symptoms of withdrawal, such as autonomic arousal, sleep disturbance, muscle tension and anxiety. Beginning on Day -2, medications listed in Table 6 will be provided to subjects as a standing regimen during the residential phase of the study (see Table 4). In the event that a subject is admitted for the residential stay early (on Days -5, -4, or -3), the ancillary medication regimen will begin as soon as the subject becomes residential. If needed for AE treatment or prophylaxis, ancillary medications may be initiated at the clinician's discretion on or after Day -5. Because mild symptoms of withdrawal may be present for several days after the VIVITROL injection, subjects will continue using ancillary medications on a modified schedule (see Table 4) through Day 11 (or, for 3 days after VIVITROL injection).

Ancillary medications are commercially available and should be stored according to package insert instructions.

Table 6: Ancillary Medications

Medication	Dose Regimen	
	Days -2 to 7	**Days 8/8a-11**[a]
Clonidine	0.1 mg oral tablet, 2 times a day	0.1 mg oral tablet, 1 time a day (only AM dose)
Clonazepam	0.5 mg oral tablet, 2 times a day	0.5 mg oral tablet, 1 time a day (only AM dose)
Trazodone hydrochloride	100 mg oral tablet, at bedtime	100 mg oral tablet, at bedtime

[a] For subjects receiving VIVITROL on Day 8/8a, ancillary medications will be reduced on Days 9 through 11, as indicated.

Subjects will also be provided with a supply of sports hydration drink, which they will be encouraged to drink liberally.

8.9.3. Concomitant Medications

Prescribed psychoactive medications, including anxiolytics and antidepressants, will be allowed for the duration of the study provided the dose is stable at the time of the screening visit.

8.9.4. Contraception and Pregnancy

All male and female subjects must agree to use an acceptable method of contraception for the duration of the study unless they are surgically sterile or postmenopausal (see below). The following are considered acceptable methods of contraception:

- Double-barrier protection (such as a condom with spermicide or a diaphragm with spermicide)
- Intrauterine device (IUD)
- Hormonal contraceptives (such as birth control pills or patches, a vaginal ring or a contraceptive implant); oral contraceptives should be initiated at least 30 days prior to Screening

Subjects who are abstinent are eligible, provided they agree to use an acceptable contraceptive method should they become sexually active.

Subjects who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone a hysterectomy, bilateral tubal ligation or bilateral salpingo-oophorectomy are considered surgically sterile. Men who have undergone a vasectomy are considered surgically sterile. Partner vasectomy is not considered an approved acceptable method of contraception for a female subject.

Women who are postmenopausal are also exempt from the requirement to use contraception. For the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to screening in women who are 45 years of age or older.

If a subject becomes pregnant while participating in the study, she will be discontinued from study drug immediately. The early termination and safety follow-up visits will be scheduled and the pregnancy will be reported to Alkermes. Additional follow-up may be required. Pregnancies in female partners of male subjects should also be reported and will be followed in the same manner.

A Pregnancy Report Form must be submitted to Alkermes (per Section 12.5) immediately, within 24 hours of awareness of the pregnancy, irrespective of whether an AE has occurred. The pregnancy will be followed until completion or termination. If the outcome of the pregnancy meets the criteria for classification as an SAE, it should be reported following the SAE procedure (see Section 12.5).

8.10. Residential Period

Subjects will be confined to a residential unit for 9 to 11 days (Days -2 to 8/8a); the residential period may be longer for subjects who are admitted to the residential unit earlier during the BUP Lead-in Period, or for subjects who fail the naloxone challenge on Day 8/8a and remain on the residential unit per Investigator judgment.

9. TREATMENT OF SUBJECTS

9.1. Investigational Product, Dosage, Duration and Mode of Administration

Naltrexone will be supplied at the doses specified in Table 3 and provided as tablets for oral administration. Naltrexone will be administered as 2 doses, given at least 1 hour apart, on Days 1 to 7.

9.2. Reference Therapy, Dosage, Duration and Mode of Administration

Placebo naltrexone (PBO-N) tablets will match the naltrexone drug product and will be administered as 2 doses, given at least 1 hour apart, on Days 1/1a to 7.

Sublingual BUP (up to 4 mg) will be administered daily to all subjects during the BUP Lead-in Period (Days -5 to -1). On Days 1/1a to 7, BUP dose will be tapered (see Table 3).

9.3. Treatment Adherence

Clinical study staff will administer study drug on an inpatient basis and record compliance for each subject in the relevant source document(s).

9.4. Randomization/Method of Assigning Subjects to Treatment

Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: naltrexone + BUP or PBO-N + BUP, stratified according to low (<8 mg/day) vs. high (8 mg/day) BUP maintenance dose at the time of initiation of the BUP Lead-in Period. The naltrexone or PBO-N assignment will be blinded while the BUP dose will be open-label. A randomization schedule will be prepared by an independent biostatistician and uploaded into an Interactive Web Response System (IWRS). The pharmacist or designee will contact the IWRS, which will assign the subject to a treatment group according to the next available randomization record. The unblinded site pharmacist or designee will dispense naltrexone or placebo for administration to subjects.

9.5. Blinding

This is a double blind study. All Alkermes staff, clinical staff and subjects will be blinded to treatment assignment until database lock. At each study site, study medications will be prepared by an unblinded research pharmacist who has no contact with participants in the trial. The investigator is responsible for all trial-related medical decisions. If the investigator deems it necessary to break the study blind in the interest of a subject's medical safety, he or she must make every effort to contact the sponsor medical monitor before the blind is broken. If the site is unable to contact the medical monitor prior to breaking the blind, the medical monitor must be contacted within 24 hours following disclosure of study drug assignment.

Breaking the blind for a single subject will not affect the blind for the remaining subjects.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Naltrexone for oral administration will be provided as white caplet-shaped IR tablets in the following dosages: 0.25, 0.5, 1.5, 3, 7.5 and 15 mg. Daily naltrexone doses are described in Table 3 with total daily doses ranging from 0.5 to 30 mg.

Placebo to match naltrexone drug product (PBO-N) will be provided as white caplet-shaped IR tablets.

Commercially available BUP will be supplied at the doses specified in Table 3 as a rapidly disintegrating tablet for sublingual administration. Buprenorphine will be administered in up to 4 mg daily dose during the lead-in (Days -5 to -1). The dose will then taper down to zero mg during the transitional dosing period leading up to the naloxone challenge (Days 1-7).

Commercially manufactured 1 mg/mL naloxone will be supplied by Alkermes as 2 mL single-dose prefilled syringes with 21 G × 1½ needles.

VIVITROL 380 mg will be supplied by Alkermes in single-use kits, each containing a 380 mg vial of VIVITROL microspheres and the diluent for suspension.

10.2. Packaging and Storage

Naltrexone tablets and placebo to match naltrexone tablets (PBO-N) will be supplied in 30-count bottles. The primary packaging consists of 60-cc high density polyethylene (HDPE) bottles heat sealed with a 1.1 g desiccant and polypropylene cap. The material should be stored at not more than 25°C.

All commercially available products are to be stored according to the manufacturer's recommendations.

Buprenorphine, a Schedule III narcotic, must be stored in accordance with US restrictions related to controlled substances.

10.3. Accountability

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study as well as through IWRS. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

Buprenorphine, a Schedule III narcotic, should be accounted for in accordance with the requirements of the Controlled Substances Act.

10.4. Handling and Disposal

Following completion and verification of accountability logs, all unused and used products must be destroyed according to applicable local and federal regulations. Alternatively, the sponsor may arrange for destruction with a third-party vendor operating in accordance with GCP and/or Good Manufacturing Practice (GMP), as applicable. Buprenorphine, as a Schedule III narcotic, should be handled and disposed of in accordance with the requirements of the Controlled Substances Act.

10.5. Management of Ancillary Medications

The ancillary medications are commercially available and should therefore be stored according to manufacturer instructions. Clonazepam is a Schedule IV controlled substance and should therefore be stored in accordance with US restrictions on controlled substances and should be accounted for, handled and disposed of in accordance with the requirements of the Controlled Substances Act.

11. ASSESSMENT OF EFFICACY

Efficacy will be assessed via the following:

- COWS score
- SOWS score
- Desire for opioids using a VAS
- PGART

Exploratory Endpoints:

The following exploratory assessments (described in detail in Section 8.8) will be conducted:

- Pupil diameter (measured during clinical testing sessions)
- QSUI
- HAM-D
- BAC Symbol Coding test
- COWA task
- WMS-III SS test
- CPT
- TAP

12. ASSESSMENT OF SAFETY

Safety and tolerability will be assessed via the following:

- AEs
- Vital signs and arterial oxygen saturation (measured during clinical testing sessions)
- Laboratory test results
- ECG parameters (uncorrected QT, QT interval corrected for heart rate using the Fridericia formula [QTcF], QT interval corrected for heart rate using the Bazett formula [QTcB], HR, RR, and QRS intervals)
- C-SSRS scores

12.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that subject and is considered clinically significant.

If the severity of a subject's withdrawal symptoms necessitates administering a nonstudy medication, or doses of an ancillary medication that exceed the standing regimen, the condition being treated should be noted as an AE.

Illnesses present prior to the subject signing the informed consent form (ICF) are considered to be pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 8.9.4, the pregnancy, including a partner's pregnancy, must be reported to Alkermes, and additional follow-up may be required.

12.2. Definition of Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality that meets one or more of the following criteria:

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life threatening or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require intervention to prevent one of the other outcomes listed above.

Admission to a hospital or an inpatient unit for a non-medical reason (ie, social stay admission) during the study in the absence of untoward medical occurrence will not be considered as an SAE, but will be captured as an AE.

Hospitalization due to worsening of behavioral health-related issues should be reported as an SAE.

12.3. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the investigator (or designated sub-investigator) according to his/her best clinical judgment. The criteria listed in Table 7 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table.

Table 7: Adverse Event Causality Guidelines

Relationship	Criteria for assessment
Definitely related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
Probably related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
Possibly related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
Probably not related	There is evidence of exposure to the test drug. AND There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
Definitely not related	The subject did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

12.4. Monitoring and Recording of Adverse Events

AE data collection will begin after a subject signs the ICF and will continue until completion of the final safety follow-up visit (Visit 10) or 28 days after the final dose of study drug. Any AE or SAE having an onset after the safety follow-up visit will not be collected or reported unless the investigator feels that the event may be related to the study drug.

Subjects will be instructed by the investigator or designee to report the occurrence of any AE. All volunteered, elicited and observed AEs are to be recorded on the AE eCRFs.

The investigator will assess all AEs regarding any causal relationship to the study drug (see Section 12.3), the intensity (severity) of the event, action taken and subject outcome.

The following criteria should be used to guide the assessment of intensity (severity):

- **Mild:** Causes awareness of sign or symptom, but is easily tolerated; does not interfere with usual activities
- **Moderate:** Causes discomfort enough to interfere with usual activities
- **Severe:** Is incapacitating; results in inability to work or perform usual activities

All AEs will be followed until resolution, until deemed stable by the investigator or until the subject is deemed by the investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure will be used as the reference document to designate event expectedness.

Withdrawal from the study as a result of an AE and any therapeutic measures that are taken shall be at the discretion of the investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the investigator or until the subject is deemed by the investigator to be lost to follow-up.

12.5. Reporting of Serious Adverse Events and Pregnancy

All SAEs and pregnancies must be reported to Alkermes via immediately, within 24 hours of discovery, by emailing: PPD PPD or by faxing the report to the following:

FAX Number: PPD

The written report for SAEs should be submitted on the SAE form provided for this purpose. The SAE report must include the Investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably or definitely related to study drug, evidence to support this assessment must also be provided.

The written report for pregnancies in female subjects and in female partners of male subjects should be submitted on the Pregnancy Report Form provided for this purpose.

13. STATISTICS

13.1. Sample Size Considerations

The primary efficacy endpoint of the study is the proportion of subjects who receive and tolerate VIVITROL injection on Day 8/8a as demonstrated by mild (COWS ≤12 or SOWS ≤10) opioid withdrawal symptoms following VIVITROL administration.

Assuming the proportion of subjects receiving and tolerating VIVITROL administration is 90% in Group 1 and 60% in Group 2, a sample size of approximately 46 subjects per treatment group will provide at least 90% power to detect a statistically significant difference between the two treatment groups at 5% level of significance in a 2-sided test.

13.2. General Statistical Methodology

In general, summary statistics (ie, n, mean, standard deviation, median, minimum and maximum for continuous variables, and number [%] of subjects in each category for categorical variables) will be provided by treatment group for all variables.

Baseline values are defined as any nonmissing assessments prior to receiving the first dose of naltrexone or PBO-N.

Source data for the summary tables and statistical analyses will be presented as by-subject data listings.

13.2.1. Study Populations

13.2.1.1. Safety Population

The safety population is defined as all randomized subjects who receive at least 1 dose of naltrexone or PBO-N.

13.3. Demographics and Baseline Data

Demographics and baseline characteristics such as gender, age, race, weight and baseline will be summarized by treatment group for the safety population.

Medical history will be summarized for the safety population using the number of observations and percentage of subjects reporting each category.

13.4. Efficacy Analyses

Efficacy analyses will be performed using the safety population.

All statistical tests will be 2-sided with a type I error rate of 5%, unless otherwise specified.

13.4.1. Primary Efficacy Endpoint

- The proportion of subjects who receive and tolerate VIVITROL injection on Day 8/8a as demonstrated by mild (COWS ≤12 or SOWS≤10) opioid withdrawal symptoms following VIVITROL administration

The analyses will be carried out using logistic regression with treatment as a factor.

13.4.2. Key Secondary Efficacy Endpoint

- Proportion of days with COWS peak score ≤12 during the Treatment Period prior to the VIVITROL injection (Days 1/1a-7)

The analysis will be carried out using a negative binomial model with treatment as a factor.

13.4.3. Other Secondary Endpoints

- Proportion of post-VIVITROL days (Days 9-11) in which subjects in each group demonstrate mild (COWS ≤12) opioid withdrawal

The analyses will be carried out using a negative binomial model with treatment as a factor.

- Mean peak COWS scores during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)
- Area under the curve (AUC) for COWS scores during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)
- Mean score for "desire for opioids" VAS during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)

These endpoints will be analyzed using an analysis of variance (ANOVA), with treatment as a factor.

13.4.4. Exploratory Endpoints

- Number and proportion of subjects in PGART response category at the end of the post-VIVITROL observation period (Day 11)

The analyses will be carried out using a logistic regression model with treatment as a factor.

- Change from baseline in pupil diameter following study drug administration during the Treatment Period (Days 1/1a-7)
- Change in frequency of substance use from screening to Day 36 assessed via the QSUI
- AUC for SOWS scores during the Treatment Period and VIVITROL Induction and Post-VIVITROL Observation Period (Days 1/1a-11)
- Change from baseline in the standardized T scores for cognitive assessments

The analyses will be carried out using an analysis of covariance (ANCOVA) with treatment as a factor.

13.5. Safety and Tolerability Analyses

Safety analyses will be performed using the safety population.

Safety and tolerability will be evaluated based on AEs, vital sign and oxygen saturation measurements, laboratory test results, ECG findings and C-SSRS scores.

Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of treatment-emergent AEs will be summarized by treatment group and overall by system organ class, and preferred terms within each system organ class. SAEs and AEs resulting in treatment discontinuation will also be summarized. AEs occurring during the treatment period preceding the naloxone challenge will be analyzed separately from AEs occurring on or after the naloxone challenge day.

Change from baseline in laboratory tests, vital signs and oxygen saturation, and ECG assessments (uncorrected QT, QTcF, QTcB, HR, RR and QRS intervals) will be summarized by treatment group and overall at each visit. Number (percentage) of subjects with potentially clinically significant (PCS) values at any postbaseline visit will be also summarized by treatment group.

For each ideation/behavior type in C-SSRS, as well as the overall ideation/behavior category, the number and percentage of subjects with 'Yes' responses at any post baseline visit (including unscheduled visit) will be summarized by treatment group.

Number and percent of subjects initiating concomitant medications, including ancillary medications, during the induction period will be summarized.

Concomitant medications will be categorized and presented using the World Health Organization (WHO) drug Anatomical Therapeutic Chemical (ATC) classification system.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes monitor or designee.

14.2. Audits and Inspections

By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority and/or an institutional review board (IRB) may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of an Alkermes audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, subjects' medical records) to determine whether these activities were conducted, and data recorded, analyzed and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements.

The investigator should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

14.3. Institutional Review Board

The investigator must obtain IRB approval for the investigation. Initial IRB approval as well as all materials approved by the IRB for this study, including the subject consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness and compliance, the study site should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 14.2 for details regarding the audit process.

15.1. Case Report Forms

This study will use eCRFs. All eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Alkermes monitor or designated representative.

The Alkermes monitor or designated representative will review all source records on-site and compare them to the data collected on the eCRF.

15.2. Confidentiality of Data

By signing this protocol, the investigator affirms to Alkermes that he or she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Alkermes. Please refer to the Clinical Study Agreement (CSA) for details.

16. ETHICAL CONSIDERATIONS

16.1. Ethics Review

The clinical site's IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling subjects into the study; written approval from the committee must be received by Alkermes before drug will be released to the investigator. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulatory requirements require.

The investigator is responsible for submitting all protocol changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

All relevant correspondence from the IRB will be forwarded by the respective study site to the sponsor in a timely fashion.

16.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the ICH Guideline E6, and all applicable local regulatory requirements. GCP is an international ethical and scientific quality standard used for designing, conducting, recording and reporting studies involving the participation of human subjects. Alkermes is committed to complying with this standard to provide assurance that the rights, safety and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

16.3. Written Informed Consent

The investigator (or authorized designee) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he/she must sign the ICF before any study-specific procedures are conducted.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB, the CRO, if applicable, and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing, or is withdrawn from investigation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and approved by the IRB, and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF must be given to the subject.

17. DATA HANDLING AND RECORDKEEPING

An overview of study data handling and recordkeeping procedures and restrictions is provided in the subsequent sections; please refer to the CSA for further details.

17.1. Data Capture

As stated in Section 15.1, this study will use eCRFs for capturing data. All entries, corrections and alterations will be made by the investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

All electronic source data collected outside the eCRF, such as results from computer- or paper-based cognitive assessments and the central laboratory, will be transferred directly to Alkermes for incorporation into the final data sets. A paper copy of all laboratory reports will remain with the source documents at the study site. All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

AEs will be coded using MedDRA. Concomitant medications will be categorized using the WHO-ATC classification system.

17.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct.

17.3. Retention of Records

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

17.4. Use of Information and Publication Policy

Data generated in this study are proprietary information that is the sole property of Alkermes. Results of the study are to be held in confidence by both the investigators and the sponsor.

Please refer to the CSA for details on the procedures for publishing and presenting data.

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APPENDICES

APPENDIX A. MINI-INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.0

FOR

DSM-5

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SAMPLE

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-5	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	❒			
		Past	❒			
		Recurrent	❒			
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	❒	296.20-296.26 Single	F32.x	❒
		Past	❒	296.20-296.26 Single	F32.x	❒
		Recurrent	❒	296.30-296.36 Recurrent	F33.x	❒
B	SUICIDALITY	Current (Past Month)	❒			❒
		Lifetime attempt	❒	❒ Low ❒ Moderate ❒ High		❒
	SUICIDE BEHAVIOR DISORDER	Current	❒	(In Past Year)		❒
		In early remission	❒	(1 - 2 Years Ago)		❒
C	MANIC EPISODE	Current	❒			
		Past	❒			
	HYPOMANIC EPISODE	Current	❒			
		Past	❒	❒ Not Explored		
	BIPOLAR I DISORDER	Current	❒	296.41-296.56	F31.0--F31.76	❒
		Past	❒	296.41-296.56	F31.0- F31.76	❒
	BIPOLAR II DISORDER	Current	❒	296.89	F31.81	❒
		Past	❒	296.89	F31.81	❒
	BIPOLAR DISORDER UNSPECIFIED	Current	❒	296.40/296.50	F31.9	❒
		Past	❒	296.40/296.50	F31.9	❒
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.44/296.54	F31.2/31.5	❒
		Past	❒	296.44/296.54	F31.2/31.5	❒
D	PANIC DISORDER	Current (Past Month)	❒	300.01	F41.0	❒
		Lifetime	❒	300.01	F40.0	❒
E	AGORAPHOBIA	Current	❒	300.22	F40.00	❒
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	❒	300.23	F40.10	❒
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	❒	300.3	F42	❒
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	❒	309.81	F43.10	❒
I	ALCOHOL USE DISORDER	Past 12 Months	❒	303.9	F10.10-20	❒
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.1x-F19.288	❒
K	PSYCHOTIC DISORDERS	Lifetime	❒	297.3/297.9/ 293.81/298.83/298.89	F20.81-F29	❒
		Current	❒	297.3/297.9/ 293.81/298.83/298.89	F20.81-F29	❒
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	❒	296.24/296.34-296.44 296.54	F31.2/F32.2/F33.3	❒
		Current	❒	296.24/296.34/296.44/296.54	F31.2/F32.2/F33. 3	❒
L	ANOREXIA NERVOSA	Current (Past 3 Months)	❒	307.1	F50.01-02	❒
M	BULIMIA NERVOSA	Current (Past 3 Months)	❒	307.51	F50.2	❒
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	❒	307.51	F50.8	❒
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	❒	300.02	F41.1	❒
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		❒ No	❒ Yes	❒ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	❒	301.7	F60.2	❒

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

SAMPLE

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. Clinicians can use it, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

- At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
- At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis or diagnoses is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, questions J2b or K6b).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.
The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:
PPD
University of South Florida College of Medicine
tel : PPD
e-mail : PPD

SAMPLE

A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** IN THE DIAGNOSTIC BOX, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, or felt sad, empty or hopeless most of the day, nearly every day, for two weeks? IF NO, CODE NO TO **A1b**: IF **YES** ASK:	NO	YES
	b	For the past two weeks, were you depressed or down, or felt sad, empty or hopeless most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks? IF NO, CODE NO TO **A2b**: IF **YES** ASK:	NO	YES
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
		➡ IS **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **A1b** AND **A2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

Over that two week period, when you felt depressed or uninterested:

		Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF **YES** TO EITHER, CODE **YES.**	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? Did anyone notice this?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day? IF **YES**, ASK FOR EXAMPLES**.** LOOK FOR DELUSIONS OF FAILURE, OF INADEQUACY, OF RUIN OR OF GUILT, OR OF NEEDING PUNISHMENT OR DELUSIONS OF DISEASE OR DEATH OR NIHILISTIC OR SOMATIC DELUSIONS. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes	NO	YES	NO	YES
f	Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly think about death **(FEAR OF DYING DOES NOT COUNT HERE),** or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? IF **YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4	Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

SAMPLE

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? N/A NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED YES FOR THAT TIME FRAME?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO	**YES**
MAJOR DEPRESSIVE EPISODE	
CURRENT	☐
PAST	☐
RECURRENT	☐

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

SAMPLE

B. SUICIDALITY

In the past month did you:

				Points
B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose?	NO	YES	0
	IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:			
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Think (even momentarily) that you would be better off dead or wish you were dead or needed to be dead?	NO	YES	1
B3	Think (even momentarily) about harming or of hurting or of injuring yourself - with at least some intent or awareness that you might die as a result - or think about suicide (i.e. about killing yourself)?	NO	YES	6

IF NO TO B2 + B3, SKIP TO B4. OTHERWISE ASK:

Frequency		Intensity	
Occasionally	☐	Mild	☐
Often	☐	Moderate	☐
Very often	☐	Severe	☐

B4	Hear a voice or voices telling you to kill yourself or have dreams with any suicidal content? If YES, was it either or both: ☐ was it a voice or voices? ☐ was it a dream?	NO	YES	4
B5	Have a suicide method in mind (i.e. how)?	NO	YES	8
B6	Have a suicide means in mind (i.e. with what)?	NO	YES	8
B7	Have any place in mind to attempt suicide (i.e. where)?	NO	YES	8
B8	Have any date/timeframe in mind to attempt suicide (i.e. when)?	NO	YES	8
B9	Think about any task you would like to complete before trying to kill yourself? (e.g. writing a suicide note)	NO	YES	8
B10	Intend to act on thoughts of killing yourself? If YES, mark either or both: ☐ did you intend to act at the time? ☐ did you intend to act at some time in the future?	NO	YES	8
B11	Intend to die as a result of a suicidal act? If YES, mark either or both: ☐ did you intend to die by suicide at the time? ☐ did you intend to die by suicide at some time in the future?	NO	YES	8
B12	Feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? If YES, mark either or both: ☐ was this to kill yourself? ☐ was this to plan to kill yourself? If YES, mark either or both: ☐ was this largely unprovoked? ☐ was this provoked?	NO	YES	8

IN ASSESSING WHETHER THIS WAS LARGELY UNPROVOKED ASK: "5 minutes before this Impulse, could you have predicted it would occur at that time?"

SAMPLE

B13	Have difficulty resisting these impulses?	NO	YES	8
B14	Take any active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO B14, SKIP TO B15.	NO	YES	
B14a	Take active steps to prepare to kill yourself, but you **did not start** the suicide attempt?	NO	YES	9
B14b	Take active steps to prepare to kill yourself, but then **you stopped yourself just before** harming yourself ("aborted").	NO	YES	10
B14c	Take active steps to prepare to kill yourself, but then **someone or something stopped you just before** harming yourself ("interrupted")?	NO	YES	11
B15	Injure yourself on purpose without intending to kill yourself?	NO	YES	0
B16	Attempt suicide (to kill yourself)? IF NO TO B16, SKIP TO B17.	NO	YES	
B16a	Start a suicide attempt (to kill yourself), but then **you decided to stop** and did not finish the attempt?	NO	YES	12
B16b	Start a suicide attempt (to kill yourself), but then **you were interrupted** and did not finish the attempt?	NO	YES	13
B16c	Went through with a suicide attempt (to kill yourself), **completely** as you meant to? A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die. IF NO, SKIP TO B17:	NO	YES	14

Hope to be rescued / survive ☐
Expected / intended to die ☐

B17 **TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS:**
Usual time spent per day: ____ hours ____ minutes.
Least amount of time spent per day: ____ hours ____ minutes.
Most amount of time spent per day: ____ hours ____ minutes.

In your lifetime:

B18	Did you ever make a suicide attempt (try to kill yourself)? If YES, how many times? _____ If YES, when was the last suicide attempt?	NO	YES	4

Current: within the past 12 months ☐
In early remission: between 12 and 24 months ago ☐
In remission: more than 24 months ago ☐

"A suicide attempt is any self injurious behavior, with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him-or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. For example, it is defined as a suicide attempt if it is clearly not an accident or if the individual thinks the act could be lethal, even though denying intent." (FDA Guidance for Industry Suicidal Ideation and Behavior Document 2012 and C-CASA definition). Posner K et al. Am J Psychiatry 2007; 164 (7): 1035-1043 & http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/

B19	How likely are you to try to kill yourself within the next 3 months on a scale of 0-100% _____% ANY LIKELIHOOD > 0% ON B19 SHOULD BE CODED YES	NO	YES	13

SAMPLE

IS AT LEAST **1** OF THE ABOVE (EXCEPT B1) CODED **YES**?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B19) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE CATEGORY AS INDICATED IN THE DIAGNOSTIC BOX:

INDICATE WHETHER THE SUICIDALITY IS CURRENT (PAST MONTH) OR A LIFETIME SUICIDE ATTEMPT OR BOTH BY MARKING THE APPROPRIATE BOXES OR BY LEAVING EITHER OR BOTH OF THEM UNMARKED. CURRENT = ANY POSITIVE RESPONSE IN B1a THROUGH B16C OR ANY TIME SPENT IN B17. LIFETIME ATTEMPT = B18 CODED YES.
LIKELY IN THE NEAR FUTURE = B19 CODED YES.

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO **YES**

SUICIDALITY

1-8 points Low ☐
9-16 points Moderate ☐
≥ 17 points High ☐

CURRENT ☐

LIFETIME ATTEMPT ☐

LIKELY IN NEAR FUTURE ☐

IS **B18** CODED YES?

AND A YES RESPONSE TO

Was the suicidal act started when the subject not in a state of confusion or delirium?

AND A YES RESPONSE TO

Was the suicidal act done without a political or religious purpose?
IF YES, SPECIFY WHETHER THE DISORDER IS CURRENT, IN EARLY REMISSION OR IN REMISSION.

NO **YES**

SUICIDAL BEHAVIOR DISORDER

CURRENT

Current ☐
In early remission ☐
In remission ☐

SAMPLE

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic-depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF YES, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' and so active or full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy or increased activity; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE NO TO **C1b**: IF **YES** ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE NO TO **C2b**: IF **YES** ASK:

b Are you currently feeling persistently irritable? NO YES

➡

IS **C1a** OR **C2a** CODED **YES**? NO YES

C3 IF **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** EPISODE FIRST AND THEN THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **C1b** AND **C2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

WHEN EXPLORING THE CURRENT EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over the past few days including today, when you felt high and full of energy or irritable, did you:

WHEN EXPLORING THE PAST EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over a period of a few days in the past, when you felt most high and most full of energy or most irritable, did you:

	Current Episode		Past Episode	
a Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES.	NO	YES	NO	YES
THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes; Past Episode ☐ No ☐ Yes				
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

SAMPLE

		Current Episode		Past Episode	
c	Talk too much without stopping, or felt a pressure to keep talking?	NO	YES	NO	YES
d	Notice your thoughts going very fast or running together or racing or moving very quickly from one subject to another?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless? This increase in activity may be with or without a purpose.	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 SUMMARY: WHEN RATING CURRENT EPISODE: NO YES NO YES

IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS INCLUDING C3f CODED YES?
IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS INCLUDING C3f CODED YES?

WHEN RATING PAST EPISODE:

IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS INCLUDING C3f CODED YES?
IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS INCLUDING C3f CODED YES?

CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.

C4 What is the longest time these symptoms lasted (most of the day nearly every day)?
ASSESS THIS DURATION FROM THE VERY START TO THE VERY END OF SYMPTOMS, NOT JUST THE PEAK.

a)	3 days or less	☐	☐
b)	4 days or more	☐	☐
c)	7 days or more	☐	☐

C5 Were you hospitalized for these problems? NO YES NO YES

IF YES, CIRCLE YES IN MANIC EPISODE FOR THAT TIME FRAME AND GO TO C7.

C6 Did these symptoms cause significant problems at home, at work, socially, in your relationships, at school or in some other important way? NO YES NO YES

C7 Were these symptoms associated with a clear change in the way that you previously functioned and that was different from the way that you usually are? NO YES NO YES

ARE **C3** SUMMARY AND **C7** AND (**C4c** OR **C5** OR **C6** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K8**) CODED **YES**

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	☐
PAST	☐

SAMPLE

IS **C3** SUMMARY CODED **YES** AND ARE **C5** AND **C6** CODED **NO** AND **C7** CODED **YES**,
AND IS EITHER **C4b** OR **C4c** CODED **YES?**
AND
IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?
AND
ARE ALL PSYCHOTIC FEATURES IN K1 THROUGH K8 CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS **NO.**

IF **YES** TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS **NOT EXPLORED.**

HYPOMANIC EPISODE

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

ARE **C3** SUMMARY AND **C4a** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE,
THEN CODE CURRENT HYPOMANIC SYMPTOMS AS **NO.**

IF **YES** TO PAST MANIC EPISODE OR YES TO PAST HYPOMANIC EPISODE,
THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED.**

HYPOMANIC SYMPTOMS

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

C8 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting 4 days or more (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the current episode if present)? NO YES

SAMPLE

D. PANIC DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, very frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make any significant change in your behavior because of the attacks (e.g., avoiding unfamiliar situations, or avoiding leaving your house or shopping alone, or doing things to avoid having a panic attack or visiting your doctor or the emergency room more frequently)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing or a smothering sensation?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or feel faint?	NO	YES
	i	Did you have hot flushes or chills?	NO	YES
	j	Did you have tingling or numbness in parts of your body?	NO	YES
	k	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	l	Did you fear that you were losing control or going crazy?	NO	YES
	m	Did you fear that you were dying?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**?	➡ NO	YES ***PANIC DISORDER LIFETIME***
D6		In the past month did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?	NO	YES ***PANIC DISORDER CURRENT***

SAMPLE

IS EITHER **D5** OR **D6** CODED **YES**,

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR LIFETIME.

NO **YES**

PANIC DISORDER

LIFETIME ☐
CURRENT ☐

E. AGORAPHOBIA

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult if you had a panic attack or panic-like or embarrassing symptoms, like: being in a crowd, or standing in a line (queue), being in an open space or when crossing a bridge, being in an enclosed space, when you are alone away from home, or alone at home, or traveling in a bus, train or car or using public transportation?	➡ NO	YES
	ARE 2 OR MORE **E1** SITUATIONS CODED YES?	➡ NO	YES
E2	Do these situations almost always bring on fear or anxiety?	➡ NO	YES
E3	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
E4	Is this fear or anxiety excessive or out of proportion to the real danger in the situation?	➡ NO	YES
E5	Did this avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
E6	Did these symptoms cause significant distress or problems at home, at work, socially, at school or in some other important way?	➡ NO	YES

IS **E6** CODED **YES**?

NO **YES**

AGORAPHOBIA CURRENT

SAMPLE

F. SOCIAL ANXIETY DISORDER (Social Phobia)

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed or rejected? This includes things like speaking in public, eating in public or with others, writing while someone watches, performing in front of others or being in social situations.	➡ NO	YES

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- PERFORMING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

F2	Do these social situations almost always bring on fear or anxiety?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
F4	Is this social fear or anxiety excessive or unreasonable in these social situations?	➡ NO	YES
F5	Did this social avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
F6	Did these social fears cause significant distress or interfere with your ability to function at work, at school or socially or in your relationships or in some other important way?	➡ NO	YES

IS **F6** CODED **YES**

and

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

NOTE TO INTERVIEWER: PLEASE SPECIFY IF THE SUBJECT'S FEARS ARE RESTRICTED TO SPEAKING OR PERFORMING IN PUBLIC.

NO	**YES**

SOCIAL ANXIETY DISORDER
(Social Phobia)
CURRENT

RESTRICTED TO PERFORMANCE SAD ONLY ☐

SAMPLE

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1a	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** religious obsessions.)	NO YES ↓ SKIP TO **G3**a
G1b	In the past month, did you try to suppress these thoughts, impulses, or images or to neutralize or to reduce them with some other thought or action? - (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO HOARDING, HAIR PULLING, SKIN PICKING, BODY DYSMORPHIC DISORDER, EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **G3**a
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES **obsessions**
G3a	In the past month, did you feel driven to do something repeatedly in response to an obsession or in response to a rigid rule, like washing or cleaning excessively, counting or checking things over and over, or repeating or arranging things, or other superstitious rituals?	NO YES
G3b	Are these rituals done to prevent or reduce anxiety or distress or to prevent something bad from happening and are they excessive or unreasonable?	NO YES **compulsions**

➡

ARE (**G1**a AND **G1**b AND G2) OR (**G3**a AND **G3**b) CODED **YES**? NO YES

G4 In the past month, did these obsessive thoughts and/or compulsive behaviors cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way or did they take more than one hour a day?

and

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?
(CHECK FOR ANY OC SYMPTOMS STARTING WITHIN 3 WEEKS OF AN INFECTION)

SPECIFY THE LEVEL OF INSIGHT AND IF THE EPISODE IS TIC-RELATED.

NO **YES**

O.C.D. CURRENT

INSIGHT:

- GOOD OR FAIR ☐
- POOR ☐
- ABSENT ☐
- DELUSIONAL ☐

TIC-RELATED ☐

SAMPLE

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury or sexual violence to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➡ NO	YES
H2	Starting after the traumatic event, did you repeatedly re-experience the event in an unwanted mentally distressing way, (such as in recurrent dreams related to the event, intense recollections or memories, or flashbacks or as if the event was recurring) or did you have intense physical or psychological reactions when you were reminded about the event or exposed to a similar event?	➡ NO	YES

H3	**In the past month:**			
	a	Did you persistently try to avoid thinking about or remembering distressing details or feelings related to the event ?	NO	YES
	b	Did you persistently try to avoid people, conversations, places, situations, activities or things that bring back distressing recollections of the event?	NO	YES
		ARE **1** OR MORE **H3** ANSWERS CODED **YES**?	➡ NO	YES
H4	**In the past month:**			
	a	Did you have trouble recalling some important part of the trauma? (but not because of or related to head trauma, alcohol or drugs).	NO	YES
	b	Were you constantly and unreasonably negative about yourself or others or the world?	NO	YES
	c	Did you constantly blame yourself or others in unreasonable ways for the trauma?	NO	YES
	d	Were your feelings always negative (such as fear, horror, anger, guilt or shame)?	NO	YES
	e	Have you become much less interested in participating in activities that were meaningful to you before?	NO	YES
	f	Did you feel detached or estranged from others?	NO	YES
	g	Were you unable to experience any good feelings (such as happiness, satisfaction or loving feelings)?	NO	YES
		ARE **2** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES
H5	**In the past month:**			
	a	Were you especially irritable or did you have outbursts of anger with little or no provocation?	NO	YES
	b	Were you more reckless or more self destructive?	NO	YES
	c	Were you more nervous or constantly on your guard?	NO	YES

SAMPLE

d Were you more easily startled? NO YES

e Did you have more difficulty concentrating? NO YES

f Did you have more difficulty sleeping? NO YES

➡

ARE **2** OR MORE **H5** ANSWERS CODED **YES**? NO YES

➡

H6 Did all these problems start after the traumatic event and last for more than one month? NO YES

H7 During the past month, did these problems cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way?

and

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

SPECIFY IF THE CONDITION IS ASSOCIATED WITH DEPERSONALIZATION, DEREALIZATION OR WITH DELAYED EXPRESSION.

NO **YES**

POSTTRAUMATIC STRESS DISORDER CURRENT

WITH

DEPERSONALIZATION ☐

DEREALIZATION ☐

DELAYED EXPRESSION ☐

SAMPLE

I. ALCOHOL USE DISORDER

(➡ MEANS: GO TO DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

		➡	
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	NO	YES

I2 **In the past 12 months**:

a.	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
b.	Did you repeatedly want to reduce or control your alcohol use? Did you try to cut down or control your alcohol use, but failed? IF **YES** TO EITHER, CODE **YES**.	NO	YES
c.	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
d.	Did you crave or have a strong desire or urge to use alcohol?	NO	YES
e.	Did you spend less time meeting your responsibilities at work, at school, or at home, because of your repeated drinking?	NO	YES
f.	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES
g.	Were you intoxicated more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
h.	Did you continue to use alcohol, even though it was clear that the alcohol had caused or worsened psychological or physical problems?	NO	YES
i.	Did you reduce or give up important work, social or recreational activities because of your drinking?	NO	YES
j.	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
k1.	When you cut down on heavy or prolonged drinking did you have any of the following:	NO	YES

1. increased sweating or increased heart rate, ☐
2. hand tremor or "the shakes" ☐
3. trouble sleeping ☐
4. nausea or vomiting ☐
5. hearing or seeing things other people could not see or hear or having sensations in your skin for no apparent reason ☐
6. agitation ☐
7. anxiety ☐
8. seizures ☐

IF **YES** TO 2 OR MORE OF THE ABOVE 8, CODE k1 AS **YES**.

k2.	Did you drink alcohol to reduce or avoid withdrawal symptoms or to avoid being hung-over?	NO	YES

SAMPLE

K SUMMARY: IF **YES** TO k1 OR k2, CODE **YES** NO YES

ARE **2** OR MORE **I2** ANSWERS FROM **I2a** THROUGH **12J** AND 12**K SUSUMMARY** CODED **YES**?

NO **YES**

ALCOHOL USE DISORDER

PAST 12 MONTHS

SPECIFIERS FOR ALCOHOL USE DISORDER:

MILD = 2-3 OF THE I2 SYMPTOMS
MODERATE = 4-5 OF THE I2 SYMPTOMS
SEVERE = 6 OR MORE OF THE I2 SYMPTOMS

IN EARLY REMISSION = CRITERIA NOT MET FOR BETWEEN 3 & 12 MONTHS
IN SUSTAINED REMISSION = CRITERIA NOT MET FOR 12 MONTHS OR MORE
(BOTH WITH THE EXCEPTION OF CRITERION d. – (CRAVING) ABOVE).

IN A CONTROLLED ENVIRONMENT = WHERE ALCOHOL ACCESS IS RESTRICTED

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐

IN EARLY REMISSION ☐
IN SUSTAINED REMISSION ☐

IN A CONTROLLED ENVIRONMENT ☐

SAMPLE

J. SUBSTANCE USE DISORDER (NON-ALCOHOL)

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
J1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Opiates: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Dissociative Drugs: PCP (Phencyclidine ,"Angel Dust", "Peace Pill", "Hog"), or ketamine ("Special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS? _____

FIRST EXPLORE THE CRITERIA BELOW FOR THE DRUG CLASS CAUSING THE BIGGEST PROBLEMS AND THE ONE MOST LIKELY TO MEET CRITERIA FOR SUBSTANCE USE DISORDER. IF SEVERAL DRUG CLASSES HAVE BEEN MISUSED, EXPLORE AS MANY OR AS FEW AS REQUIRED BY THE PROTOCOL.

J2 **Considering your use of (NAME OF DRUG / DRUG CLASS SELECTED), in the past 12 months:**

a.	During the times when you used the drug, did you end up using more (NAME OF DRUG / DRUG CLASS SELECTED) than you planned when you started?	NO	YES
b.	Did you repeatedly want to reduce or control your (NAME OF DRUG / DRUG CLASS SELECTED) use? Did you try to cut down or control your (NAME OF DRUG / DRUG CLASS SELECTED) use, but failed? IF **YES** TO EITHER, CODE **YES**.	NO	YES
c.	On the days that you used more (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time obtaining (NAME OF DRUG / DRUG CLASS SELECTED), using it, or recovering from the its effects?	NO	YES
d.	Did you crave or have a strong desire or urge to use (NAME OF DRUG / DRUG CLASS SELECTED)?	NO	YES
e.	Did you spend less time meeting your responsibilities at work, at school, or at home, because of your repeated (NAME OF DRUG / DRUG CLASS SELECTED) use?	NO	YES
f.	If your (NAME OF DRUG / DRUG CLASS SELECTED) use caused problems with your family or other people, did you still keep on using it?	NO	YES
g.	Did you use the drug more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
h.	Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it was clear that the (NAME OF DRUG / DRUG CLASS SELECTED) had caused or worsened psychological or physical problems?	NO	YES

SAMPLE

i. Did you reduce or give up important work, social or recreational activities because of your (NAME OF DRUG / DRUG CLASS SELECTED) use? NO YES

j. Did you need to use (NAME OF DRUG / DRUG CLASS SELECTED) a lot more in order to get the same effect that you got when you first started using it or did you get much less effect with continued use of the same amount? NO YES
THIS CRITERION IS CODED NO IF THE MEDICATION IS PRESCRIBED AND USED UNDER MEDICAL SUPERVISION.

k1. When you cut down on heavy or prolonged use of the drug did you have any of the following withdrawal symptoms: NO YES
IF **YES** TO THE REQUIRED NUMBER OF WITHDRAWAL SYMPTOMS FOR EACH CLASS, CODE J2k1 AS **YES**.
THIS CRITERION IS CODED NO IF THE MEDICATION IS PRESCRIBED AND USED UNDER MEDICAL SUPERVISION.

Sedative, Hypnotic or Anxiolytic (2 or more)
1. increased sweating or increased heart rate ☐
2. hand tremor or "the shakes" ☐
3. trouble sleeping ☐
4. nausea or vomiting ☐
5. hearing or seeing things other people could not see or hear or having sensations in your skin for no apparent reason ☐
6. agitation ☐
7. anxiety ☐
8. seizures ☐

Opiates (3 or more)
1. feeling depressed ☐
2. nausea or vomiting ☐
3. muscle aches ☐
4. runny nose or teary eyes ☐
5. dilated pupils, goose bumps or hair standing on end or sweating ☐
6. diarrhea ☐
7. yawning ☐
8. hot flashes ☐
9. trouble sleeping ☐

Stimulants (2 or more)
1. fatigue ☐
2. vivid or unpleasant dreams ☐
3. difficulty sleeping or sleeping too much ☐
4. increased appetite ☐
5. feeling or looking physically or mentally slowed down ☐

Cannabis (3 or more)
1. irritability, anger or aggression ☐
2. nervousness or anxiety ☐
3. trouble sleeping ☐
4. appetite or weight loss ☐
5. restlessness ☐
6. feeling depressed ☐
7. significant discomfort from one of the following: "stomach pain", tremors or "shakes", sweating, hot flashes, chills, headaches. ☐

SAMPLE

k2. Did you use (NAME OF DRUG / DRUG CLASS SELECTED) to reduce or avoid withdrawal symptoms? NO YES

J2k **SUMMARY**: IF **YES** TO J2k1 OR J2k2, CODE **YES** NO YES

ARE **2** OR MORE **J2** ANSWERS FROM **J2a** THROUGH **J2k SUMMARY** CODED **YES**?
(**J2**k1 AND **J2**k2 TOGETHER COUNT AS ONE AMONG THESE CHOICES)

NO **YES**

SUBSTANCE
(Drug or Drug Class Name)
USE DISORDER

PAST 12 MONTHS

SPECIFIERS FOR SUBSTANCE USE DISORDER:

MILD = 2-3 OF THE J2 SYMPTOMS
MODERATE = 4-5 OF THE J2 SYMPTOMS
SEVERE = 6 OR MORE OF THE J2 SYMPTOMS

IN EARLY REMISSION = CRITERIA NOT MET FOR BETWEEN 3 & 12 MONTHS
IN SUSTAINED REMISSION = CRITERIA NOT MET FOR 12 MONTHS OR MORE
(BOTH WITH THE EXCEPTION OF CRITERION d. – (CRAVING) ABOVE).

IN A CONTROLLED ENVIRONMENT = WHERE SUBSTANCE / DRUG ACCESS IS RESTRICTED

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐

IN EARLY REMISSION ☐
IN SUSTAINED REMISSION ☐

IN A CONTROLLED ENVIRONMENT ☐

SAMPLE

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

Now I am going to ask you about unusual experiences that some people have.

K1 a Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NO YES
NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.

b **IF YES:** do you currently believe these things? NO YES

K2 a Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking? NO YES

b **IF YES:** do you currently believe these things? NO YES

K3 a Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? NO YES
CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.

b **IF YES:** do you currently believe these things? NO YES

K4 a Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you? NO YES

b **IF YES:** do you currently believe these things? NO YES

K5 a Have your relatives or friends ever considered any of your beliefs odd or unusual? NO YES
INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS K1 TO K4, FOR EXAMPLE, RELIGIOUS, DEATH, DISEASE OR SOMATIC DELUSIONS, DELUSIONS OF GRANDIOSITY, JEALOUSY OR GUILT, OR OF FAILURE, INADEQUACY, RUIN, OR DESTITUTION, OR NIHILISTIC DELUSIONS.

b **IF YES:** do they currently consider your beliefs strange or unusual? NO YES

K6 a Have you ever heard things other people couldn't hear, such as voices? NO YES

IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other? NO YES

b **IF YES TO K6a:** have you heard sounds / voices in the past month? NO YES

IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other? NO YES

SAMPLE

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 a DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED, INCOHERENT OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K9 a DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K10 a DID THE PATIENT EVER IN THE PAST HAVE NEGATIVE SYMPTOMS, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION)? NO YES

K10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

K11 a ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K7a, CODED **YES**?

ARE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO YES
↳ **K13**

HOW LONG HAS THE MOOD EPISODE LASTED? _____
HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? _____
IF SUCH A MOOD EPISODE IS PRESENT, IT MUST BE PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE NO TO K11a.

IF NO TO K11a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO K13.

SAMPLE

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **K1**a TO **K7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER GROUPING, ALSO CIRCLE NO TO K12 AND MOVE TO K13

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

LIFETIME

K12 a ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K7b CODED **YES** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO K13 AND K14 AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

CURRENT

K13 ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K8b, CODED **YES**?

AND

ARE 2 OR MORE « b » QUESTIONS FROM K1b TO K10b, CODED **YES**?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

SAMPLE

K14 IS **K13** CODED **YES**

OR

(ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K8a, CODED **YES**?

AND

ARE 2 OR MORE « a » QUESTIONS FROM K1a TO K10a, CODED **YES**

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?)

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

NO	**YES**
	PSYCHOTIC DISORDER **LIFETIME**

SAMPLE

L. ANOREXIA NERVOSA

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

L1 a How tall are you? ☐☐ ft ☐☐ in. / ☐☐☐ cm

b. What was your lowest weight in the past 3 months? ☐☐☐ lb / ☐☐☐ kg

c IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW) ➡ NO YES

In the past 3 months:

L2 In spite of this low weight, have you tried not to gain weight or to restrict your food intake? ➡ NO YES

L3 Have you intensely feared gaining weight or becoming fat, even though you were underweight? ➡ NO YES

L4 a Have you considered yourself too big / fat or that part of your body was too big / fat? NO YES

b Has your body weight or shape greatly influenced how you felt about yourself? NO YES

c Have you thought that your current low body weight was normal or excessive? NO YES

L5 ARE 1 OR MORE ITEMS FROM **L4** CODED **YES**? ➡ NO YES

IS **L5** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.0 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lb	79	82	84	87	90	93	96	99	102	106	109	112	115	119
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	36	37	38.5	39.5	41	42.5	43.5	45.5	46.5	48	49	51	52	54

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lb	122	125	129	133	136
cm	180	183	185	188	191
kg	55	57	58.5	60	62

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.0 kg/m^2 for the patient's height using the Center of Disease Control & Prevention BMI Calculator. This is the threshold guideline below which a person is deemed underweight by the DSM-5 for Anorexia Nervosa.

SAMPLE

M. BULIMIA NERVOSA

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	NO YES ↳ **M3**
M2	During these binges, did you feel that your eating was out of control?	NO YES

M3	Did you do anything to compensate for, or to prevent a weight gain, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications? Did you do this as often as once a week? CODE YES TO M3 ONLY IF THE ANSWER TO BOTH THESE M3 QUESTIONS IS YES.	➡ NO YES
M3a	Number of Episodes of Inappropriate Compensatory Behaviors per Week? _____ Number of Days of Inappropriate Compensatory Behaviors per Week? _____	
M4	In the last 3 months, did you have eating binges as often as once a week?	➡ NO YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO YES ↓ Skip to M8
M7	Do these binges occur only when you are under (_____ lb/kg)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO YES

M8 IS **M5** CODED **YES** AND IS EITHER **M6** OR **M7** CODED **NO**?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **M7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

SAMPLE

DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?

AND

ARE M2 AND M3 CODED NO?

NO **YES**

ANOREXIA NERVOSA
Restricting Type
CURRENT

SPECIFIERS OF EATING DISORDER:

MILD = 1-3 EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
MODERATE = 4-7 EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
SEVERE = 8-13 EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
EXTREME = 14 OR MORE EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐
EXTREME ☐

MB. BINGE EATING DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO IN THE DIAGNOSTIC BOX, AND MOVE TO THE NEXT MODULE)

MB1	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	➡ YES
MB2	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR BULIMIA NERVOSA?	NO	➡ YES
MB3	M2 IS CODED YES	➡ NO	YES
MB4	M3 IS CODED YES	NO	➡ YES
MB5	M4 IS CODED YES	➡ NO	YES
	In the last 3 months during the binging did you:		
MB6a	Eat more rapidly than normal?	NO	YES
MB6b	Eat until you felt uncomfortably full?	NO	YES
MB6c	Eat large amounts of food when you were not hungry?	NO	YES
MB6d	Eat alone because you felt embarrassed about how much you were eating?	NO	YES
MB6e	Feel guilty, depressed or disgusted with yourself after binging?	NO	YES
	ARE 3 OR MORE **MB6** QUESTIONS CODED YES?	➡ NO	YES

SAMPLE

MB7 Does your binging distress you a lot? ➡ NO YES

MB8 Number of Binge Eating Episodes per Week? _____

Number of Binge Eating Days per Week? _____

IS MB7 CODED YES?

NO YES

BINGE-EATING DISORDER

CURRENT

SPECIFIERS OF EATING DISORDER:

MILD = 1-3 EPISODES OF BINGE EATING PER WEEK
MODERATE = 4-7 EPISODES OF BINGE EATING PER WEEK
SEVERE = 8-13 EPISODES OF BINGE EATING PER WEEK
EXTREME = 14 OR MORE EPISODES OF BINGE EATING PER WEEK

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐
EXTREME ☐

SAMPLE

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a worrier or a "worry wart"?) AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	➡ NO	YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES?**	➡ NO	YES
N4		Do these anxieties and worries significantly disrupt your ability to work, to function socially or in your relationships or in other important areas of your life or cause you significant distress? AND IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?	**NO**	**YES**

GENERALIZED ANXIETY DISORDER
CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines or in withdrawal from any of these?	❒ No	❒ Yes	❒ Uncertain
O1b	Did you have any medical illness?	❒ No	❒ Yes	❒ Uncertain
O2	IF O1a OR O1b IS CODED YES, IN THE CLINICIAN'S JUDGMENT IS EITHER LIKELY TO BE A DIRECT CAUSE OF THE PATIENT'S DISORDER? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.	❒ No	❒ Yes	❒ Uncertain
O2 SUMMARY: AN "ORGANIC" / MEDICAL / DRUG RELATED CAUSE BEEN RULED OUT IF **O2** IS YES, THEN **O2** SUMMARY IS NO. IF **O2** IS NO, THEN **O2** SUMMARY IS YES. OHTERWISE IT IS UNCERTAIN.		❒ No	❒ Yes	❒ Uncertain

SAMPLE

P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight or stayed out at night against your parent's rules?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal or break into someone's house or car?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone into sexual activity?	NO	YES ➡

ARE **2** OR MORE **P1** ANSWERS CODED **YES**? NO YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

P2 **Since you were 15 years old, have you:**

a	done things that are illegal or would be grounds to get arrested, even if you didn't get caught (for example destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
b	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
c	been impulsive and didn't care about planning ahead?	NO	YES
d	been in physical fights repeatedly or assaulted others (including physical fights with your spouse or children)?	NO	YES
e	exposed others or yourself to danger without caring?	NO	YES
f	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
g	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	**YES**
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

◗ THIS CONCLUDES THE INTERVIEW

SAMPLE

MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:
- A Major Depressive Episode
- C (Hypo)manic Episode
- K Psychotic Disorders

MODULE K:

1a	IS **K11b** CODED YES?	NO	YES
1b	IS **K12a** CODED YES?	NO	YES

MODULES A and C:		Current	Past
2	a CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7**	YES	YES
	b CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7**	YES	YES

c Is Major Depressive Episode coded YES (current or past)?
and
is Manic Episode coded NO (current and past)?
and
is Hypomanic Episode coded NO (current and past)?
and
is **"**Rule out Organic Cause (O2 Summary)" coded YES?

Specify:
- If the depressive episode is **current** or **past** or both
- **With Psychotic Features** Current: If 1b or 2a (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) = YES

MAJOR DEPRESSIVE DISORDER

	current	past
MDD	❑	❑

With Psychotic Features

Current	❑
Past	❑

SAMPLE

d Is a Manic Episode coded YES (current or past)?

Specify:

- If the Bipolar I Disorder is **current** or **past** or both
- With **Single Manic Episode**: If Manic episode (current or past) = YES and MDE (current and past) = NO
- **With Psychotic Features** Current: If 1b or 2a (current) or 2b (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) or 2b (past) = YES
- If the **most recent episode** is manic, depressed, or hypomanic or unspecified (all mutually exclusive)
- **Most Recent Episode Unspecified** if the Past Manic Episode is coded YES

AND

(If any current C3 symptoms are coded YES and current C3 Summary is coded NO)

OR

(If current C3 Summary is coded YES
AND
If current Manic Episode diagnostic box is coded NO current)

BIPOLAR I DISORDER

	current	past
Bipolar I Disorder	❑	❑
Single Manic Episode	❑	❑

With Psychotic Features

Current	❑
Past	❑

Most Recent Episode

Manic	❑
Depressed	❑
Hypomanic	❑
Unspecified	❑

Most Recent Episode

Mild	❑
Moderate	❑
Severe	❑

e Is Major Depressive Episode coded YES (current or past)
and
Is Hypomanic Episode coded YES (current or past)
and
Is Manic Episode coded NO (current and past)?

Specify:

- If the Bipolar Disorder is **current** or **past** or both
- If the most recent mood episode is **hypomanic** or **depressed** (mutually exclusive)
- **Most Recent Episode Unspecified** if the Past Manic / Hypomanic Episode is coded YES

AND

(If any current C3 symptoms are coded YES and current C3 Summary is coded NO)

OR

(If current C3 Summary is coded YES
AND
If current Hypomanic Episode diagnostic box is coded NO current)

BIPOLAR II DISORDER

	current	past
Bipolar II Disorder	❑	❑

Most Recent Episode

Hypomanic	❑
Depressed	❑
Hypomanic	❑
Unspecified	❑

Most Recent Episode

Mild	❑
Moderate	❑
Severe	❑

SAMPLE

f Is MDE coded NO (current and past)
and
Is Manic Episode coded NO (current and past)
and
Is C4b coded YES for the appropriate time frame
and
Is C8b coded YES?

---

or

Is Manic Episode coded NO (current and past)
and
Is Hypomanic Episode coded NO (current and past)
and
Is C4a coded YES for the appropriate time frame
and
Is C8c coded YES?

Specify if the Bipolar Disorder Unspecified is **current** or **past** or both.

BIPOLAR DISORDER UNSPECIFIED

	current	past
Bipolar Disorder Unspecified	❑	❑

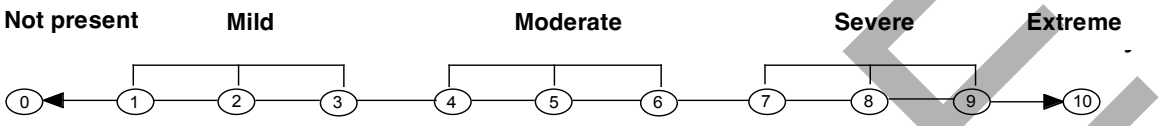
SAMPLE

OPTIONAL ASSESSMENT MEASURES TO TRACK CHANGES OVER TIME

A: CROSS CUTTING MEASURES

SEVERITY OF SYMPTOM

Use this scale to rate the severity of your symptom in the score column in the table below:



Assessment of Symptoms That Cut Across Disorders

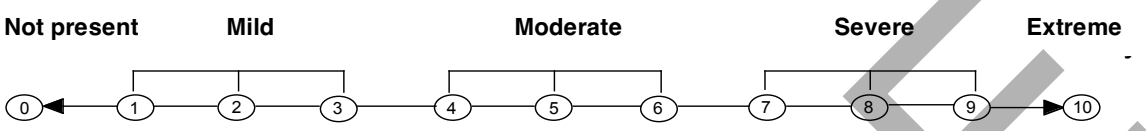
	Symptom Name	Score
1	Depression	
2	Anger	
3	Mania (feeling up or high or hyper or full of energy with racing thoughts)	
4	Anxiety	
5	Physical (somatic) symptoms	
6	Suicidal thoughts (having ANY thoughts of killing yourself)	
7	Hearing sounds or voices others can't hear or fearing someone can hear or read your thoughts or believing things others don't accept as true e.g. that people are spying on you or plotting against you or talking about you (Psychosis)	
8	Sleep problems	
9	Memory problems	
10	Repetitive thoughts or behaviors	
11	Feeling things around you are strange, unreal, detached or unfamiliar, or feeling outside or detached from part or all of your body (Dissociation)	
12	Ability to function at work, at home, in your life, or in your relationships (Personality functioning)	
13	Overusing alcohol or drugs	

SAMPLE

B: DISABILITY / FUNCTIONAL IMPAIRMENT

SEVERITY OF DISABILITY / IMPAIRMENT

Use this scale to rate in the score column of the table below, how much your symptoms have disrupted your ability to function in the following areas of your life:



Assessment of Impairment of Functioning /Disability

	Domain Name	Score
1	Work or school work	
2	Social life or leisure activities (like hobbies or things you do for enjoyment)	
3	Family life and / or home responsibilities	
4	Ability to get along with people	
5	Personal and social relationships	
6	Ability to understand and to communicate with others	
7	Ability to take care of yourself (washing, showering, bathing, dressing properly, brushing teeth, laundry, combing / brushing hair, eating regularly)	
8	Made you disruptive or aggressive towards others	
9	Financially (ability to manage your money)	
10	Ability to get around physically	
11	Spiritual or religious life	
12	How much did your condition have an impact on other people in your family?	

SAMPLE

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SAMPLE

M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI. The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME		
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent		
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)		
	MDE WITH CATATONIC FEATURES	Current (2 weeks)		
	MDE WITH ATYPICAL FEATURES	Current (2 weeks)		
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past		
	MINOR DEPRESSIVE DISORDER (DEPRESSIVE DISORDER UNSPECIFIED)	Current (2 weeks) Past Recurrent		
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past		
	SUBSTANCE INDUCED MOOD DISORDER	Current (2 weeks) Past		
AY	DYSTHYMIA	Current		
B	SUICIDALITY	Current (Past Month) Lifetime attempt	❒ ❒	❒ Low ❒ Moderate ❒ High
	SUICIDE BEHAVIOR DISORDER	Current In early remission	❒ ❒	(In Past Year) (1 - 2 Years Ago)
C	MANIC EPISODE	Current Past		
	HYPOMANIC EPISODE	Current Past		
	BIPOLAR I DISORDER	Current Past		
	BIPOLAR II DISORDER	Current Past		
	BIPOLAR DISORDER UNSPECIFIED	Current Past		
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past		
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past		
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past		
	SUBSTANCE INDUCED MANIC EPISODE	Current (2 weeks)		

SAMPLE

		Past
	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current (2 weeks) Past
	MOOD DISORDER UNSPECIFIED	Lifetime
D	PANIC DISORDER	Current (Past Month) Lifetime
	ANXIETY DISORDER WITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current
E	AGORAPHOBIA	Current
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month) Generalized Non-Generalized
FA	SPECIFIC PHOBIA	Current
G	OBSESSIVE-COMPULSIVE DISORDER (OCD)	Current (Past Month)
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED OCD	Current
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
HL	POSTTRAUMATIC STRESS DISORDER	Lifetime
I	ALCOHOL USE DISORDER	Past 12 Months
IL	ALCOHOL USE DISORDER	Lifetime
J	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months
JL	SUBSTANCE USE DISORDER (Non-alcohol)	Lifetime
K	PSYCHOTIC DISORDERS	Lifetime Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current
	SCHIZOPHRENIA	Current Lifetime
	SCHIZOAFFECTIVE DISORDER	Current Lifetime
	SCHIZOPHRENIFORM DISORDER	Current Lifetime
	BRIEF PSYCHOTIC DISORDER	Current Lifetime
	DELUSIONAL DISORDER	Current Lifetime
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current Lifetime
	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current Lifetime

SAMPLE

	PSYCHOTIC DISORDER UNSPECIFIED	Current Lifetime
L	ANOREXIA NERVOSA	Current (Past 3 Months)
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
M	BULIMIA NERVOSA	Current (Past 3 Months)
	BULMIA NERVOSA, PURGING TYPE	Current
	BULMIA NERVOSA, NON-PURGING TYPE	Current
MB	BINGE-EATING DISORDER	Current (Past 3 Months)
N	GENERALIZED ANXIETY DISORDER (GAD)	Current (Past 6 Months)
	GAD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED GAD	Current
O	SOMATIZATION DISORDER	Current Lifetime
P	HYPOCHONDRIASIS	Current
Q	BODY DYSMORPHIC DISORDER	Current
R	PAIN DISORDER	Current
S	CONDUCT DISORDER	Current (past 12 months)
T	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Children /Adolescents)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
TA	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Adults)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
U	PREMENSTRUAL DYSPHORIC DISORDER	Current
V	MIXED ANXIETY DEPRESSIVE DISORDER	Current
W	ADJUSTMENT DISORDERS	Current
X	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT	
Y	ANTISOCIAL PERSONALITY DISORDER	Lifetime

For Schizophrenia and psychotic disorder studies and for psychotic disorder subtyping in clinical settings, use the MINI for Psychotic Disorders instead of the standard MINI. For many clinical settings this level of psychotic disorder subtyping detail is not necessary.
For children and adolescents, use the MINI Kid or the MINI Kid Parent of the MIN Kid for Psychotic Disorders.
A computerized version of the MINI is available from Medical Outcomes Systems https://www.medical-outcomes.com

SAMPLE

SAMPLE

APPENDIX B. COLUMBIA-SUICIDE SEVERITY RATING SCALE

- Baseline/Screening
- Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

SAMPLE

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact PPD *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* PPD

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

	Most Severe	Most Severe
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____	____

SAMPLE

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

SAMPLE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

SAMPLE

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact PPD *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* PPD

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead — Yes ☐ No ☐

Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

2. Non-Specific Active Suicidal Thoughts — Yes ☐ No ☐

General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — Yes ☐ No ☐

Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*
Have you been thinking about how you might do this?

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — Yes ☐ No ☐

Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — Yes ☐ No ☐

Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Frequency — ____

How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration — ____

When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability — ____

Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents — ____

Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation — ____

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

SAMPLE

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

SAMPLE

APPENDIX C. CLINICAL OPIATE WITHDRAWAL SCALE

Clinical Opiate Withdrawal Scale (COWS)

Daily Assessments Days -5 to 11/Follow-up (Morning and Evening during Residential Days -2 to 7, Morning Only Day 8/8a)

For each item, write in the number that best describes the patient's signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Subject ID:_____ Date: _____	
Time: (eg,15:00) 24-hour clock	
Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	
Restlessness *Observation during assessmen*t 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	

SAMPLE

Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting	
Tremor *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching	
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute	
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult	
Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
Total score : The total score is the sum of all 11 items	
Rater Initials:	

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
More than 36 = severe withdrawal

SAMPLE

Clinical Opiate Withdrawal Scale (COWS)

Clinical Testing Sessions (Days 1/1a-7)

Note: Day 14 session is paired with VIVITROL injection and only extends 60 min postdose.
For each item, write in the number that best describes the patient's signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Subject ID:_____ Date: _____	Predose	30 Min Postdose	60 Min Postdose	90 Min Postdose	120 Min Postdose	150 Min Postdose	180 Min Postdose
Time: (eg,15:00) 24-hour clock							
Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120							
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face							
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds							
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible							
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort							

SAMPLE

Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks							
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting							
Tremor *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching							
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute							
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult							
Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection							
Total scores The total score is the sum of all 11 items							
Rater Initials							

SAMPLE

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
More than 36 = severe withdrawal

Clinical Opiate Withdrawal Scale (COWS)

Day 8/8a – Naloxone Challenge/VIVITROL Injection

For each item, write in the number that best describes the patient's signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Subject ID:_____ Date: _____		Challenge, Part 1		Challenge, Part 2		
	Predose	10 Min Postdose Part 1	20 Min Postdose Part 1	10 Min Postdose Part 2	20 Min Postdose Part 2	1 Hour Postdose VIVITROL
Times: (eg, 15:00) 24-hour clock						
Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120						
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face						
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds						
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible						
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort						

SAMPLE

Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks						
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting						
Tremor *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching						
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute						
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult						
Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection						
Total scores The total score is the sum of all 11 items						
Rater Initials						
Same rater as previous? (Y/N)	N/A					

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
More than 36 = severe withdrawal

SAMPLE

APPENDIX D. SUBJECTIVE OPIATE WITHDRAWAL SCALE

ALKERMES ALK6428-A302			
Subject Initials:	Site No. / Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Time Performed (24 hours)
		____/____/____	____:____

SOWS

Instructions: Please complete a survey each evening.
Answer the following statements as accurately as you can, circling the answer that best fits the way you feel now.

0 = not at all
1 = a little
2 = moderately
3 = quite a bit
4 = extremely

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1	I feel anxious.	0	1	2	3	4
2	I feel like yawning.	0	1	2	3	4
3	I'm perspiring.	0	1	2	3	4
4	My eyes are tearing.	0	1	2	3	4
5	My nose is running.	0	1	2	3	4
6	I have goose flesh.	0	1	2	3	4
7	I am shaking.	0	1	2	3	4
8	I have hot flashes.	0	1	2	3	4
9	I have cold flashes.	0	1	2	3	4
10	My bones and muscles ache.	0	1	2	3	4
11	I feel restless.	0	1	2	3	4
12	I feel nauseous.	0	1	2	3	4
13	I feel like vomiting.	0	1	2	3	4
14	My muscles twitch.	0	1	2	3	4
15	I have cramps in my stomach.	0	1	2	3	4
16	I feel like shooting up now.	0	1	2	3	4

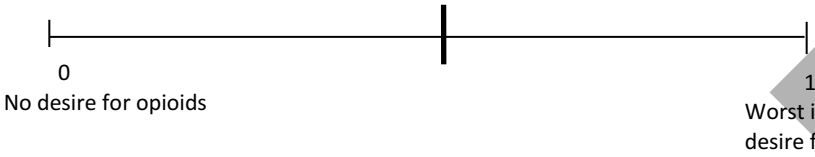
SAMPLE

APPENDIX E. DESIRE FOR OPIOIDS VISUAL ANALOGUE SCALE

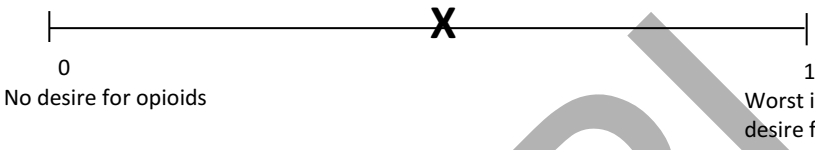
Desire for Opioids VAS

Instructions: Below is a question regarding your desire for opioids. We would like to know how strong your desire for opioids has been over the past 24 hours. Please place a vertical line (**I**) somewhere on the line between **0** and **100** to indicate how strong your desire for opioids has been over the past 24 hours.

Correct:



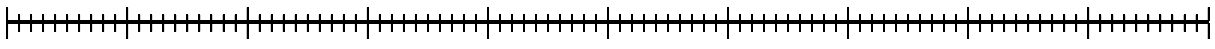
Incorrect:



If you make a mistake, cross out your answer, initial and date it, and place a new vertical mark on the line.

Please indicate how strong your desire for opioids has been over the past 24 hours below:

Your own desire for opioids



0
No Desire for Opioids

100
Strongest Imaginable Desire for Opioids

SAMPLE

APPENDIX F. SHORT MICHIGAN ALCOHOL SCREENING TEST

SHORT MICHIGAN ALCOHOL SCREENING TEST (SMAST)

NAME: _____ Date:_____

The following questions concern information about your involvement with alcohol during the past 12 months. Carefully read each statement and decide if your answer is "YES" or "NO". Then, circle the appropriate answer beside the question.

Please answer every question. If you have difficulty with a statement, then choose the response that is mostly right.

These questions refer to the past 12 months only.

Please circle the appropriate answer.

1.	Do you feel you are a normal drinker? (by normal we mean do you drink less than or as much as most other people.)	Yes No
2.	Do your wife, husband, a parent or other near relative ever worry or complain about your drinking?	Yes No
3.	Do you ever feel guilty about your drinking?	Yes No
4.	Do friends or relatives think you are a normal drinker?	Yes No
5.	Are you always able to stop drinking when you want to?	Yes No
6.	Have you ever attended a meeting of Alcoholics Anonymous (AA)?	Yes No
7.	Has drinking ever created problems between you and your wife, husband, a parent or other near relative?	Yes No
8.	Have you ever gotten into trouble at work because of drinking?	Yes No
9.	Have you ever neglected your obligations, your family, or your work for 2 or more days in a row because you were drinking?	Yes No
10.	Have you ever gone to anyone for help about your drinking?	Yes No
11.	Have you ever been in the hospital because of drinking?	Yes No
12.	Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?	Yes No
13.	Have you ever been arrested, even for a few hours, because of other drunken behaviors?	Yes No

*** SMAST Score_____**

** See scoring instructions for correct scoring procedures*

SAMPLE

SHORT MICHIGAN ALCOHOL SCREENING TEST (SMAST)

Administration & Interpretation

Instructions

From: A Self-Administered Short Michigan Alcohol Screening Test (SMAST)
M.L. Seltzer, A. Vinokur, and L.J. Van Rooijen. Studies on Alcohol 36:117-126, 1975

The Short Michigan Alcohol Screening Test (SMAST) is a 13-item questionnaire that requires a 7th grade reading level, and only a few minutes to complete. It was developed from the Michigan Alcoholism Screening Test. Evaluation data indicate that it is an effective diagnostic instrument, and does not have a tendency for false positives, as does the Michigan Alcoholism Screening Test. It is strongly recommended that the DAST-10 be used along with the SMAST unless there is a clear indication that the client uses alcohol but does not use any other drug at all.

The SMAST is self-administered. All questions are to be answered with “YES” or “NO” answers only. A "No" answer to questions 1,4, and 5, and each "Yes" response to the other questions earn one point.

Interpretations: A score of 1 or 2 indicates that there is no alcohol problem and no further action is needed at this time. A score of 3 indicates a borderline alcohol problem and further investigation is necessary.

SAMPLE

SMAST Score	Degree of Problem Alcohol Involvement	Suggested Action
0-2	No problems reported	None at this time.
3	Borderline alcohol problem reported	Further investigation is required.
4 or more	Potential Alcohol Abuse reported	A full assessment is required.

APPENDIX G. QUANTITATIVE SUBSTANCE USE INVENTORY

IRB #6374 – PPD -Principal Investigator

Pt. Study ID: _____ **Date:** _____

Rater Initials: _____ **Study Week #:**_____

Title (circle): Participant Physician Nurse **Study Visit #:**_____

Psychiatrist Therapist RA IR

QUANTITATIVE SUBSTANCE USE INVENTORY

Day Start: _____
Day End: _____

1. Number of Days Assessed 1. _____

2. Opiate Use

   a. # days on which opiates used 2a. _____

   b. Average $ value of opiates used per day of opiate use 2b. _____

   c. Maximum $ value opiates used per day of opiate use 2c. _____

   d. Principal route of opiate use 2d. _____

   (0=NA; 1=PO; 2-IN; 3=SC; 4=IV)

   e. # days on which urge, desire, or craving for opiates occurred 2e. _____

   f. Opiate craving 2f. _____

   'In the past week did you crave heroin (opiates) or have the urge to use it? How strong was the urge? How hard was it to resist?'

   0=none
   1=mild urges, easily resisted
   2=moderate urges, requiring effort to resist
   3=strong urges to use, difficult to resist
   4=severe, usually impossible to resist urges to use

3. Cocaine use

   a. # days on which cocaine used 3a. _____

   b. Average $ value of cocaine used per day of cocaine use 3b. _____

   c. Maximum $ value cocaine used per day of cocaine use 3c. _____

   d. Principal route of cocaine use 3d. _____
   (0=NA; 2=IN; 3=FB/crack; 4=IV)

   e. Number of days on which urge, desire, or craving for cocaine occurred 3e. _____

   f. Cocaine craving 3f. _____

   'In the past week did you crave cocaine or have the urge to use it? How strong was the urge? How hard was it to resist?'

   0=none
   1=mild urges, easily resisted
   2=moderate urges, requiring effort to resist
   3=strong urges to use, difficult to resist
   4=severe, usually impossible to resist urges to use

SAMPLE

QUANTITATIVE SUBSTANCE USE INVENTORY—CLINICIAN RATED
(Page 2 of 2)

4. Other drug or alcohol use number of days of use of each of the following:

a. alcohol 4a. _____

drinks/drinking day _____

b. cannabis (marijuana, hashish, etc) 4b. _____

c. benzodiazepines 4c. _____

d. other sedatives/hypnotics 4d. _____

e. stimulants 4e. _____

f. PCP (angel dust) 4f. _____

g. hallucinogens 4g. _____

h. other 4h. _____

i. # days which urge, desire, or craving for other drug or alcohol 4i. _____

j. Other drug or alcohol craving 4j. _____

'In the past week did you crave (other drug/alcohol) or have the urge to use it? How strong was the urge? How hard was it to resist?'

0=none
1=mild urges, easily resisted
2=moderate urges, requiring effort to resist
3=strong urges to use, difficult to resist
4=severe, usually impossible to resist urges to use

5. Summary Drug Use

a. # days using any illicit drugs 5a. _____

b. # days using heroin, cocaine, or both 5b. _____

c. # days using any IV or SC 5c. _____

d. # days with urge, desire, or craving for any drug 5d. _____

e. Overall drug craving 5e. _____

'In the past week did you crave drugs in general or have the urge to use them? How strong was the urge? How hard was it to resist?'

0=none
1=mild urges, easily resisted
2=moderate urges, requiring effort to resist
3=strong urges to use, difficult to resist
4=severe, usually impossible to resist urges to use

SAMPLE

APPENDIX H. PATIENT GLOBAL ASSESSMENT OF RESPONSE TO THERAPY

PATIENT GLOBAL ASSESSMENT OF RESPONSE TO THERAPY (PGART)

How would you rate your response to the medication that you received during the study? Please check one of the following:

☐ Poor

☐ Fair

☐ Good

☐ Very Good

☐ Excellent

SAMPLE

APPENDIX I. STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON RATING SCALE FOR DEPRESSION

STRUCTURED INTERVIEW GUIDE
FOR THE HAMILTON DEPRESSION SCALE (SIGH-D)

Janet B.W. Williams, D.S.W.

INTERVIEWER

The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information.

Time period. The interview questions indicate that the ratings should be based on the patient's condition in the past week.

Referent of "usual" or "normal" condition. Several of the interview questions in the HAM-D refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

This instrument provides an interview guide for both the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiat 23:56-61, 1960). The anchor point descriptions for both scales, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). Additional designators were added in parentheses to the depression scale anchor points by Kobak, Lipsitz and Williams to further standardize ratings. A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747).

For further information contact PPD at PPD

Revised 21 February 2007.

SAMPLE DO NOT USE

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Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?		
	___ ___ : ______	Yes □ No □ N/A □ 1st administration of this instrument to this subject		
Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.	
		___ ___/___ ___ ___/_________ ___		

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION SCALE (SIGH_D)*

OVERVIEW: **I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?**

What's your mood been like this past week (compared to when you feel OK)? Have you been feeling down or depressed? IF YES: Can you describe what this feeling has been like for you? How bad is the feeling? Does the feeling lift at all if something good happens? How are you feeling about the future? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all?	**DEPRESSED MOOD** (sadness, hopeless, helpless, worthless): 0 - absent 1 - indicated only on questioning*(occasional, mild depression)* 2 - spontaneously reported verbally *(persistent, mild to moderate depression)* 3 - communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep *(persistent, moderate to severe depression,)* 4 - VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication *(persistent, very severe depression, with extreme hopelessness or tearfulness)*

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

NOTES:

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	__ __ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this subject

Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/_____ ___	

How have you been spending your time this past week (when not at work)? Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them? How much less interested in these things have you been this past week compared to when you're not depressed? How hard to do you have to push yourself to do them? Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why? About how many hours a day do you spend doing things that interest you? Is there anything you look forward to? IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do? How much less productive or efficient are you compared to before you were depressed?	**WORK AND ACTIVITIES:** 0 - no difficulty 1 - thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies *(Mild reduction in interest or pleasure; no clear impairment in functioning)* 2 - loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities; (*Clear reduction in interest, pleasure or functioning)* 3 - decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (hospital job or hobbies) exclusive of ward chores (*Profound reduction in interest, pleasure, or functioning)* 4 - stopped working bec. of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (*Unable to work or fulfill primary role because of illness, and total loss of interest)*
Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began? **When have you been falling asleep and waking up over the past week?**	
Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?) How many nights this week have you had trouble falling asleep? Have you changed the time at which you try to get to sleep since you've been depressed?	**INSOMNIA EARLY (INITIAL INSOMNIA):** 0 - no difficulty falling asleep 1 - complains of occasional difficulty falling asleep (i.e., more than 1/2 hour, *2-3 nights)* 2 - complains of nightly difficulty falling asleep *(i.e., more than ½ hour, 4 or more nights)*

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Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?
	__ __ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this subject

Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/_____ ___	

During the past week, have you been waking up in the middle of the night? IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?) When you get back in bed, are you able to fall right back asleep? How long does it take you to fall back asleep? Do you wake up more than once during the night? (If yes: How long does it take for you to fall back to sleep each time?) Have you felt your sleeping has been restless or disturbed some nights? How many nights this week have you had that kind of trouble?	**INSOMNIA MIDDLE:** 0 - no difficulty 1 - complains of being restless and disturbed during the night (or *Occasional difficulty, i.e., 2-3 nights, more than ½ hr)* 2 - waking during the night - any getting out of bed (except to void) (*Often i.e., 4 or more nights of difficulty, more than ½ hr)*
What time have you been waking up in the morning for the last time, this past week? IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, when you feel well)? How many mornings this past week have you awakened early?	**INSOMNIA LATE (TERMINAL INSOMNIA):** 0 - no difficulty 1 - waking in early hours of morning but goes back to sleep *(occasional, i.e., 2-3 nights difficulty)* 2 - unable to fall asleep again if gets out of bed *(often, i.e., 4 or more nights difficulty)*
Sometimes, along with depression or anxiety, people might lose interest in sex. This week, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.) Has there been any change in your interest in sex (from when you were feeling OK)? IF YES: How much less interest do you have compared to when you're not depressed? (Is it a little less or a lot less?)	**GENITAL SYMPTOMS** (such as loss of libido, menstrual disturbances): 0 - absent 1 - mild (*Somewhat less interest than usual)* 2 - severe (*A lot less interest than usual)*

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Rater Initials			Time Performed (24 hours)								Has the rater changed from the previous assessment?		
			___ ___ : ______								Yes ◻ No ◻ N/A ◻ 1st administration of this instrument to this subject		
Subject Initials:			Subject ID No.								Date of Assessment (DD/MMM/YYYY)	Visit No.	
											___ ___/___ ___ ___/_________ ___		

How has your appetite been this past week? (What about compared to your usual appetite?) IF LESS: How much less than usual? Have you had to force yourself to eat? Have other people had to urge you to eat? (Have you skipped meals?)	**SOMATIC SYMPTOMS GASTROINTESTINAL:** 0 - none 1 - loss of appetite but eating without encouragement (*Appetite somewhat less than usual)* 2 - difficulty eating without urging (or *Appetite significantly less than usual)*
Have you lost any weight since this (DEPRESSION) began? IF YES: Did you lose any weight this last week? (Was it because of feeling depressed or down?) How much did you lose? IF NOT SURE: Do you think your clothes are any looser on you? AT FOLLOW-UP: Have you gained any of the weight back? IF YES: How much? **NOTE: RATE 1 TO 3 ONLY IF PATIENT LOST WEIGHT AND HAS NOT BEGUN TO GAIN IT BACK.**	**LOSS OF WEIGHT (Rate either A or B):** A. When rating by history: 0 - no weight loss 1 - probable weight loss due to current depression 2 - definite (according to patient) weight loss due to depression 3 - not assessed B. On weekly ratings by ward staff, when actual weight changes are measured: 0 - less than 1 lb. loss in week 1 - more than 1 lb. loss in week 2 - more than 2 lb. loss in week 3 - not assessed **NOTE: AVOID CODING "3" IF POSSIBLE**

SAMPLE - DO NOT USE

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Rater Initials			Time Performed (24 hours)								Has the rater changed from the previous assessment?		
			___ ___ : ______								Yes □ No □ N/A □ 1st administration of this instrument to this subject		
Subject Initials:			Subject ID No.								Date of Assessment (DD/MMM/YYYY)	Visit No.	
											___ ___/___ ___ ___/_________ ___		

How has your energy been this past week? IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?) This week, have you had any aches or pains? (What about backaches or muscle aches?) (How much of the time? How bad has it been?) Have you felt any heaviness in your limbs, back, or head?	**SOMATIC SYMPTOMS GENERAL:** 0 - none 1 - heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatiguability. *(Somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)* 2 - any clear-cut symptoms *(Persistent, significant loss of energy or muscle aches/heaviness)*
Have you been putting yourself down this past week, feeling you've done things wrong, or let others down? IF YES: What have your thoughts been? Have you been feeling guilty about anything that you've done or not done? IF YES: What have your thoughts been? What about things that happened a long time ago? IF UNKNOWN: How often have you thought about this the past week? Have you thought that you've brought (THIS DEPRESSION) on yourself in some way? (Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)	**FEELINGS OF GUILT:** 0 - absent 1 - self-reproach, feels he has let people down 2 - ideas of guilt or rumination over past errors or sinful deeds *(feelings of guilt, remorse or shame)* 3 - present illness is a punishment. Delusions of guilt. (severe, pervasive feelings of guilt) 4 - hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

SAMPLE - DO NOT USE

Rater Initials			Time Performed (24 hours)								Has the rater changed from the previous assessment?		
			___ ___ : ______								Yes □ No □ N/A □ 1st administration of this instrument to this subject		
Subject Initials:			Subject ID No.								Date of Assessment (DD/MMM/YYYY)		Visit No.
											___ ___/___ ___ ___/__________ ___		

This past week, have you had thoughts that life is not worth living? IF YES: What about thinking you'd be better off dead? Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?	**SUICIDE:** 0 - absent 1 - feels life is not worth living 2 - wishes he were dead or any thoughts of possible death to self 3 - suicidal ideas of gesture 4 - attempts at suicide
Have you been feeling especially tense this past week? IF YES: Is this more than is normal for you? Have you been unusually argumentative or impatient? Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example? How often have you felt this way the past week? Has this caused you any problems or difficulties? IF YES: Like what, for example?	**ANXIETY PSYCHIC:** 0 - no difficulty 1 - subjective tension and irritability *(Mild, occasional)* 2 - worrying about minor matters (*Moderate, causes some distress)* 3 - apprehensive attitude apparent in face or speech (*Severe; significant impairment in functioning due to anxiety)* 4 - fears expressed without questioning (*Symptoms incapacitating)*

SAMPLE - DO NOT USE

Rater Initials			Time Performed (24 hours)									Has the rater changed from the previous assessment?	
			___ ___ : ______									Yes □ No □ N/A □ 1st administration of this instrument to this subject	
Subject Initials:			Subject ID No.									Date of Assessment (DD/MMM/YYYY)	Visit No.
												___ ___/___ ___ ___/_________ ___	

Tell me if you've had any of the following physical symptoms in the past week. (READ LIST) FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you this past week? (How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?) NOTE: DO NOT RATE SXS THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.	**ANXIETY SOMATIC** (physiologic concomitants of anxiety, such as GI - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Resp - hyperventilating, sighing Urinary frequency Sweating): 0 - not present 1 - mild *(Symptom(s) present only infrequently, no impairment, minimal distress)* 2 - moderate (*Symptom(s) more persistent, or some interference with usual activities, moderate distress)* 3 - severe *(Significant impairment in functioning)* 4 - incapacitating
In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?) Have you worried a lot that you had a specific medical illness? Do you complain much about how you feel physically? Have you seen a doctor about these problems? What did the doctor say?	**HYPOCHONDRIASIS:** 0 - not present 1 - self-absorption (bodily) (*Some inappropriate worry about his/her health OR slightly concerned despite reassurance)* 2 - preoccupation with health *(Often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance)* 3 - frequent complaints, requests for help, etc. *(Is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health)* 4 - hypochondriacal delusions

SAMPLE - DO NOT USE

Rater Initials			Time Performed (24 hours)								Has the rater changed from the previous assessment?			
			___ ___ : ______								Yes □ No □ N/A □ 1st administration of this instrument to this subject			
Subject Initials:			Subject ID No.								Date of Assessment (DD/MMM/YYYY)		Visit No.	
											___ ___/___ ___ ___/_________ ___			

RATING BASED ON OBSERVATION DURING INTERVIEW	**INSIGHT:** 0 - acknowledges being depressed and ill OR not currently depressed 1 - acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc. 2 - denies being ill at all
RATING BASED ON OBSERVATION DURING INTERVIEW	**AGITATION:** 0 - none 1 - fidgetiness (slight agitation or mild restlessness) 2 - playing with hands, hair, etc. (moderate to marked restlessness or agitation) 3 - moving about, can't sit still (cannot remain seated) 4 - hand-wringing, nail biting, hair-pulling, biting of lips (interview cannot be conducted; severe agitation)
RATING BASED ON OBSERVATION DURING INTERVIEW	**RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity): 0 - normal speech and thought 1 - slight retardation at interview (mild psychomotor retardation) 2 - obvious retardation at interview (moderate; some difficulty with interview, noticeable pauses and slowness of thought) 3 - interview difficult (severe psychomotor retardation; very long pauses) 4 - complete stupor (extreme retardation; interview barely possible)

SAMPLE - DO NOT USE

TOTAL HAM-D SCORE:	__________

Rater Signature: ______________________ Date: ________________________

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APPENDIX J. BRIEF ASSESSMENTS OF COGNITION SYMBOL CODING TEST

If the respondent completes the sample item correctly and in a manner that shows he or she understands what to do, say: **Good! Let's try the next one.** Turn to the test page.

Administration of Test

Say: **On this page are numbers from 1 to 25. Do this the same way. Begin at number one** [point], **and draw a line from one to two** [point to "2"], **two to three** [point to "3"], **three to four** [point "4"], **and so on, in order until you reach the end** [point]. **Remember, work as fast as you can. Ready? Begin!**

Start timing. If the respondent makes an error, call it to his or her attention immediately, and have the respondent proceed from the point the mistake occurred. Do not stop timing.

If the respondent completes Part A without error, remove the test sheet. Record the time in seconds. Errors count only in the increased time of performance.

Scoring

Record the total time for completion in seconds in the score space to the right.

Discontinue the test after 300 seconds, regardless of whether the subject is finished or not.

TEST 1

TMT Score:

(Time in seconds; maximum = 300)

Sample

Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS SC)

Test 2

(Allow 90 seconds.)

Administration of Test

Turn to the correct page in the MCCB Respondent's Booklet. Read the following to the respondent:
Look at the boxes at the top of this page. Notice that each mark is unique and that each has a different number beneath it. Now look at these boxes down here (point). **There are marks in the top part, but the bottom box is empty. Your task is to fill in the corresponding number beneath each mark. For example, here is the first mark** (point to the first example). **When I look up at the key, I see that this mark has a 1 beneath it, so I fill in a 1 down here** (write a 1 for the first example). **The next mark has a 5 beneath it, so down here I fill in a 5** (write in a 5 for the second example). **Next is this mark; on the key here is a 2 beneath it** (write in the 2). **Now you do the rest of these examples up to this heavy line.** The respondent should use a pencil without an eraser or a pen. Correct the respondent if any mistakes are made. **Good! Do you have any questions?** Answer any questions. **If you make a mistake you cannot erase, but you can write over the number that you wrote. OK, working as quickly as you can, fill in the numbers that match the marks. Work across the rows from left to right** (point), **without skipping any. Ready?** Make certain that the respondent is on task and prepared to start with pencil in hand before go is said. **Go.** Start the stopwatch immediately after saying go.

Stop the respondent after 90 seconds.

Scoring

Place the BACS SC scoring template (provided in the kit) over the page of the Respondent's Booklet on which the Symbol Coding responses are written. Circle any responses that are not correct. Subtract the number of incorrect responses from the total number of items completed in 90 seconds. Then count the number of correct responses and record this number in the space here.

TEST 2

BACS SC Score:

(Number of correct responses; maximum = 110)

Hopkins Verbal Learning Test—Revised™ (HVLT-R™)

Test 3

Administration of Test

Use the HVLT-R Test Booklet. You will be administering only the three Learning Trials, not the Delayed Recall Trial. After this test has been administered, attach the completed HVLT-R Form to the MCCB Administrator's Form. Write the Form number in the Test 3 box on this page.

Scoring

Tally the number of *correctly* reported words. Correct minor errors in pronunciation (e.g., "cimmonim" for "cinnamon") or pluralization (e.g., "rubies" for "ruby") as they occur, but count these responses as correct. Self-corrections are also considered correct. Unambiguous paraphasias (e.g., "cabbage" for "lettuce" and "motel" for "hotel") are considered errors and not counted in the trial score.

The number of words correctly recalled by the respondent is recorded and entered in the spaces provided.

TEST 3

HVLT-R Score:

Trial 1	Trial 2	Trial 3

(Number of words recalled correctly over 3 trials; maximum = 12 for each trial)

Form Administered: ____

Sample

Wechsler Memory Scale-III (WMS III): Spatial Span

Test 4

You will be using the WMS Spatial Span Board.

Rules

Discontinue Rule

After scores of 0 on both trials of any item for both Spatial Span Forward and Spatial Span Backward. For both Spatial Span Forward and Spatial Span Backward, administer both trials of each item even if Trial 1 is passed.

Recording Rule

Write the number of each cube in the order the respondent taps it.

Scoring Rule

0–1 pt. for each trial

KEY

⊃	≡	≻	X	∧	=	*	∋	∞
1	2	3	4	5	6	7	8	9

⊃	∧	≡	⊃	≻	=	≡	X	⊃	=		≡	⊃	=	⊃	≡

X	=	⊃	≡	∧	=	≻	X	⊃	≡	=	∞	X	≻	∋

X	∧	*	∋	⊃	≻	*	X	∋	∧	≡	∞	≻	X	*

≡	X	∧	⊃	=	X	⊃	∧	=	*	∞	∋	≻	=	X

∞	∧	∋	≻	=	*	X	∧	≡	≻	*	∞	≡	∋	⊃

=	∞	*	≡	≻	=	X	∞	⊃	*	≡	∧	=	∋	X

≡	∋	*	∞	≻	*	∋	∧	⊃	∞	≡	⊃	X	≻	=

∧	≡	⊃	=	X	≡	⊃	=	∞	*	≻	∧	X	∋	∞

Sample

APPENDIX K. CONTROLLED ORAL WORD ASSOCIATION TASK

Controlled Oral Word Association Test (COWAT)

(Allow 60 seconds per trial)

INSTRUCTIONS: *Say to the patient:*

> **I will say a letter of the alphabet. Then I want you to give me as many words that begin with the letter as quickly as you can. For instance, if I say 'B', you might give me 'bad', 'battle', 'bed'... I do not want you to use words that are proper names or things that would start with a capital letter, such as 'Boston', 'Bob', or 'Buick'. Also, do not use the same word again with a different ending such as 'eat' and 'eating'. Any questions?** (pause) **Begin when I say the letter. The first letter is 'F'. You have one minute. Go ahead.**

Begin timing immediately. Allow one minute. If patients discontinue before the end of the minute, encourage them to try to think of more words. If there is a silence of 15 seconds, repeat the basic instructions:

Remember, you are to tell me as many words as you can that begin with the letter 'F'.

For scoring purposes, write down the actual words in the order in which they are produced. A score sheet for recording individual patient responses has been included on the following page. If shorthand is used, be sure to make each word legible for review. Write all words, even if they are repetitions or incorrect. If repetitions occur that may be accepted if an alternate meaning was intended by the patient, ("four" and "for", "son" and "sun"), then ask what was meant by this word at the **END** of the 1-minute period.

The first (letter-F) trial is followed by the following instruction:

> **Now tell me as many words beginning with the letter 'A' as you can. You have one minute. Ready, go.**

SAMPLE

Last, the patient is instructed:

Now tell me as many words beginning with the letter 'S' as you can. You have one minute. Ready, go.

SCORING:

Repetitions of words are not corrected but are not included in scoring. The total number of correct words generated for each letter, F, A, and S, (excluding intrusions, repeated roots or repetitions of the same word) are counted and entered on the response sheet. For example, if a patient generated 18 F-words, 12 A-words, and 20 S-words, the totals would be entered on the response sheet.

Scoring Rules

Acceptable words begin with the given letter (F, A, or S). Slang words and foreign words that are part of standard English (e.g. "amigo") are acceptable.

UNACCEPTABLE WORDS include the following:

- Words that are proper names, as indicated in the instructions. Generally, these proper names are capitalized. The following proper names would all be unacceptable: France, Fred, February, Friday, and Fritos.

- Words that sound like they belong but the actual spelling dictates that the word choice was incorrect. For example, "phone" is not acceptable as an "F" word.

- Words that are repetitions. For example, if the patient says, "feel" as the first word, then repeats it later; the patient will receive credit only for the first time the word is given. Homonyms, however, *are* acceptable if the patient indicates that the word has a different meaning from the first time it was given. For example, a patient may say "ant" and then later say "aunt". You may need to ask the patient what word was intended. Credit for both words would be given.

- Words that have the same root and basically refer to the same thing. This is sometimes difficult to judge. Words that are clearly variations of the root word are not given credit. For example, if "fast, faster, fastest" were given, credit would go only to "fast." If "flexible, flexibility" were given, credit would

SAMPLE

go only to “flexible.” In addition, the repetition of a word as a compound word is unacceptable. For example, if “air, air mattress” were given, credit would go only to “air”.

However, words that have the same root, yet refer to clearly different things, should be given credit. For example, if “fool, foolhardy” or “fireman, fireplug” were given, credit would go to both words. (These are also one word responses, not two words with the same first word.) The best rule of thumb for determining whether a word is a repetition or not is to refer to the phrase in the instructions that asks the patients not to “use the same word again with a different ending.”

Numbers pose a problem because some patients attempt to give a series of numbers. In keeping with the rules above, “five, fifty, and fifteen” would all receive credit, yet “fifty-one, fifty-two” or “five, five thousand” would receive only one point.

SAMPLE

APPENDIX L. WECHSLER MEMORY SCALE-III SPATIAL SPAN TEST

Scoring

Place the BACS SC scoring template (provided in the kit) over the page of the Respondent's Booklet on which the Symbol Coding responses are written. Circle any responses that are not correct. Subtract the number of incorrect responses from the total number of items completed in 90 seconds. Then count the number of correct responses and record this number in the space here.

TEST 2

BACS SC Score:

(Number of correct responses; maximum = 110)

Hopkins Verbal Learning Test—Revised™ (HVLT-R™)

Test 3

Administration of Test

Use the HVLT-R Test Booklet. You will be administering only the three Learning Trials, not the Delayed Recall Trial. After this test has been administered, attach the completed HVLT-R Form to the MCCB Administrator's Form. Write the Form number in the Test 3 box on this page.

Scoring

Tally the number of *correctly* reported words. Correct minor errors in pronunciation (e.g., "cimmonim" for "cinnamon") or pluralization (e.g., "rubies" for "ruby") as they occur, but count these responses as correct. Self-corrections are also considered correct. Unambiguous paraphasias (e.g., "cabbage" for "lettuce" and "motel" for "hotel") are considered errors and not counted in the trial score.

The number of words correctly recalled by the respondent is recorded and entered in the spaces provided.

TEST 3

HVLT-R Score:

Trial 1	Trial 2	Trial 3

(Number of words recalled correctly over 3 trials; maximum = 12 for each trial)

Form Administered: _____

Sample

Wechsler Memory Scale-III (WMS III): Spatial Span

Test 4

You will be using the WMS Spatial Span Board.

Rules

Discontinue Rule

After scores of 0 on both trials of any item for both Spatial Span Forward and Spatial Span Backward. For both Spatial Span Forward and Spatial Span Backward, administer both trials of each item even if Trial 1 is passed.

Recording Rule

Write the number of each cube in the order the respondent taps it.

Scoring Rule

0–1 pt. for each trial

Administration of "Forward" Section

Place the Spatial Span Board on the table with the cube numbers facing you and with the board centered at the respondent's midline so that he or she can easily reach the cubes. Say: **Now I want you to do exactly what I do. Touch the blocks I touch, in the same order.**

Tap out the sequence for Trial 1 of Spatial Span Forward Item 1 (see below) at a rate of one cube per second.

Continue administering the items for Spatial Span Forward, using the sequences below. Record the responses. If the criterion for discontinuing is met, or if all Spatial Span Forward items have been administered, proceed with Spatial Span Backward.

Item/Trial		Response	Score 0 or 1
1. Trial 1	3 – 10		
Trial 2	7 – 4		
2. Trial 1	1 – 9 – 3		
Trial 2	8 – 2 – 7		
3. Trial 1	4 – 9 – 1 – 6		
Trial 2	10 – 6 – 2 – 7		
4. Trial 1	6 – 5 – 1 – 4 – 8		
Trial 2	5 – 7 – 9 – 8 – 2		
5. Trial 1	4 – 1 – 9 – 3 – 8 – 10		
Trial 2	9 – 2 – 6 – 7 – 3 – 5		
6. Trial 1	10 – 1 – 6 – 4 – 8 – 5 – 7		
Trial 2	2 – 6 – 3 – 8 – 2 – 10 – 1		
7. Trial 1	7 – 3 – 10 – 5 – 7 – 8 – 4 – 9		
Trial 2	6 – 9 – 3 – 2 – 1 – 7 – 10 – 5		
8. Trial 1	5 – 8 – 4 – 10 – 7 – 3 – 1 – 9 – 6		
Trial 2	8 – 2 – 6 – 1 – 10 – 3 – 7 – 4 – 9		
		FORWARD Total Score: Range = 0 to 16	

Sample

Administration of "Backward" Section

Say: **Now I am going to touch some more blocks. This time when I stop, I want you to touch the blocks backward, in the reverse order of mine. For example, if I touch this block** (Cube 3), **then this one** (Cube 5), **what would you do?**

If a correct response is made, say: **That's right. Here's the next one. Remember to touch them in the reverse order.**

Then proceed with Item 1 (on the next page).

If an incorrect response is made on the 3-5 example sequence, point appropriately as you say: **No, I touched this one, then this one, so, to do it in reverse, you would touch this one, then this one. Now let's try another one. If I touch this one** (Cube 9), **then this one** (Cube 1), **what would you do?**

Whether the respondent succeeds or fails on the second example, proceed to Item 1.

Continue administering the items for Spatial Span Backward (using the sequences below) until the criterion for discontinuing is met or until all items are administered. Record the responses.

Item/Trial		(Correct Response)/Response	Score 0 or 1
1. Trial 1	7 – 4	(4 – 7)	
Trial 2	3 – 10	(10 – 3)	
2. Trial 1	8 – 2 – 7	(7 – 2 – 8)	
Trial 2	1 – 9 – 3	(3 – 9 – 1)	
3. Trial 1	10 – 6 – 2 – 7	(7 – 2 – 6 – 10)	
Trial 2	4 – 9 – 1 – 6	(6 – 1 – 9 – 4)	
4. Trial 1	5 – 7 – 9 – 8 – 2	(2 – 8 – 9 – 7 – 5)	
Trial 2	6 – 5 – 1 – 4 – 8	(8 – 4 – 1 – 5 – 6)	
5. Trial 1	9 – 2 – 6 – 7 – 3 – 5	(5 – 3 – 7 – 6 – 2 – 9)	
Trial 2	4 – 1 – 9 – 3 – 8 – 10	(10 – 8 – 3 – 9 – 1 – 4)	
6. Trial 1	2 – 6 – 3 – 8 – 2 – 10 – 1	(1 – 10 – 2 – 8 – 3 – 6 – 2)	
Trial 2	10 – 1 – 6 – 4 – 8 – 5 – 7	(7 – 5 – 8 – 4 – 6 – 1 – 10)	
7. Trial 1	6 – 9 – 3 – 2 – 1 – 7 – 10 – 5	(5 – 10 – 7 – 1 – 2 – 3 – 9 – 6)	
Trial 2	7 – 3 – 10 – 5 – 7 – 8 – 4 – 9	(9 – 4 – 8 – 7 – 5 – 10 – 3 – 7)	
8. Trial 1	8 – 2 – 6 – 1 – 10 – 3 – 7 – 4 – 9	(9 – 4 – 7 – 3 – 10 – 1 – 6 – 2 – 8)	
Trial 2	5 – 8 – 4 – 10 – 7 – 3 – 1 – 9 – 6	(6 – 9 – 1 – 3 – 7 – 10 – 4 – 8 – 5)	
		BACKWARD Total Score: Range = 0 to 16	

Sample

Scoring

For each trial, score 1 point if the exact sequence is tapped. Score 0 points if the respondent does not tap all of the specified cubes or makes an error in the tapping sequence.

TEST 4

WMS-III Spatial Span Total Score:

Range = 0 to 32

(Sum of Forward Total Score & Backward Total Score)

APPENDIX M. CONTINUOUS PERFORMANCE TEST

For the next 10 minutes we're going to measure attention and memory. You are going to see numbers flash on the screen.

(Press any key to continue.)

Sample

Some will be 4 digit numbers that look like this:

2579

(Press any key to continue.)

Some will be 3 digit numbers that look like this:

(Press any key to continue.)

Sample

and some will be 2 digit numbers that look like this:

(Press any key to continue.)

Your role is to respond whenever you see two numbers that are exactly the same flash twice in a row.

(Press any key to continue.)

To respond, press and release (click) the left mouse button as fast as you can.

(Press any key to continue.)

Sample

Let's take a look at some examples ...

(Press any key to continue.)

In this 4-digit example, there is ONE correct response:

(Press any key to continue.)

Sample

In this 4-digit example, there is ONE correct response:

3528

(Correct mouse Click)

(Press any key to continue.)

Let's take a look at another example.

(Press any key to continue.)

Sample

In this 3-digit example, there are TWO correct responses, so pay attention:

(Press any key to continue.)

Sample

In this 3-digit example, there are TWO correct responses, so pay attention:

463

(Correct Mouse Click)

In this 3-digit example, there are TWO correct responses, so pay attention:

579

(Correct mouse click)

(Press any key to continue.)

Let's take a look at another example.

(Press any key to continue.)

Sample

In this 2-digit example, there is ONE correct response:

(Correct Click)

(Press any key to continue.)

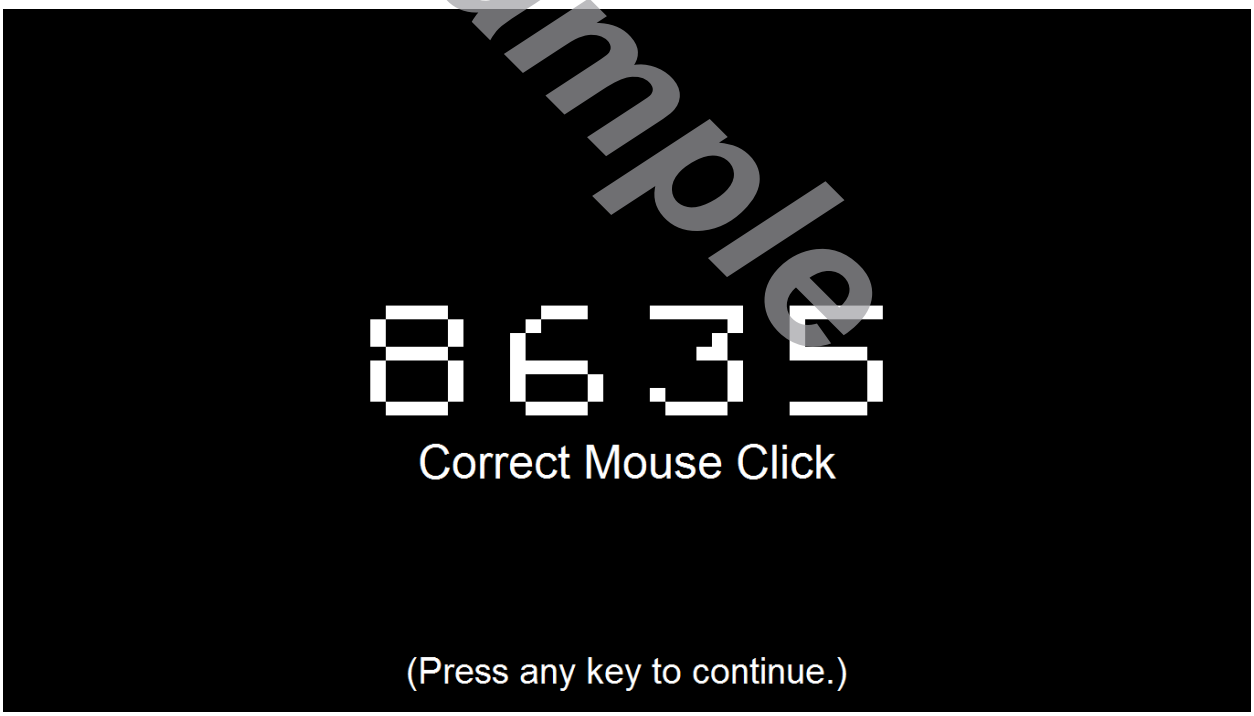
Sample

Remember, you are only to respond (click) when the number you see is EXACTLY the same as the number flashed just before.

(Press any key to continue.)


2496
DO NOT CLICK MOUSE

Sample


8635
Correct Mouse Click
(Press any key to continue.)

Now, we're going to try a few.

The numbers will flash very fast on the screen.

Remember, click (press and release) the left mouse button only when you see TWO numbers in a row that are exactly the same.

(Press any key to continue.)

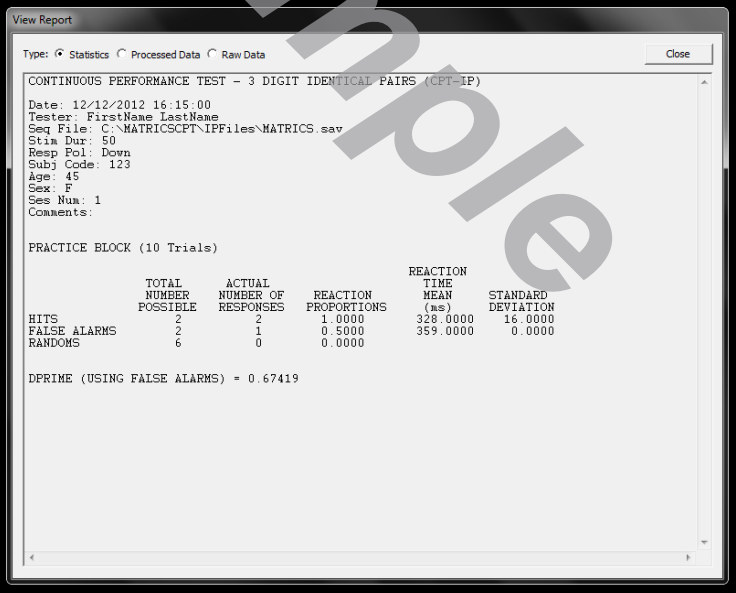
Sample

Would you like a practice block?

Begin Practice

Be sure the response button is up,
then press a key on the computer to begin.

Sample



Would you like another practice block?

Sample

Begin 2-Digit Numbers

Be sure the response button is up,
then press a key on the computer to begin.

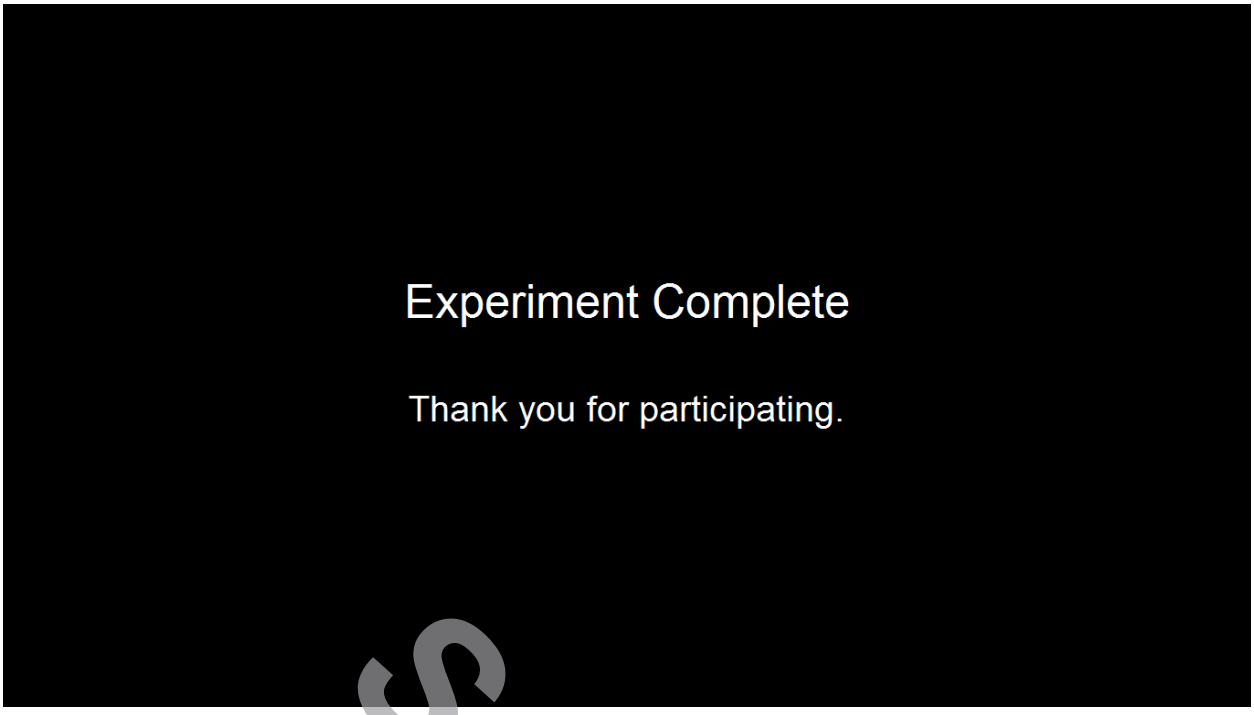
Break Before 3-Digit Numbers

To continue, be sure the response button is up,
then press a key on the computer to begin.

Sample

Break Before 4-Digit Numbers

To continue, be sure the response button is up,
then press a key on the computer to begin.



Sample

APPENDIX N.TEST OF ATTENTIONAL PERFORMANCE

Divided Attention / dual task

You have two tasks in this test:

First task:
You will see a region on the screen in which a varying number of crosses appear simultaneously. When four of these crosses form a square, then please press the key as quickly as possible.

Example:

Second task:
In this task you will hear a high and a low tone in sequence. You must decide whether the same tone occurs twice in a row. Please press the key as quickly as possible!

Your task is to pay attention to both squares and tones at the same time.

Please press a key (cancel with X)

Sample