Official Title:	**A Phase 2, Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial of Brexpiprazole (1 - 3 mg/day) as Monotherapy or as Combination Therapy in the Treatment of Adults with Post-traumatic Stress Disorder**
NCT Number:	NCT03033069
Document Dates:	Protocol Amendment 1 : 07 June 2017 Protocol Addendum Amendment 1; 8 June 2017

Protocol and/or Protocol Amendments
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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Phase 2, Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial of Brexpiprazole (1 - 3 mg/day) as Monotherapy or as Combination Therapy in the Treatment of Adults with Post-traumatic Stress Disorder

Protocol No. 331-201-00061
IND No. 117,549

CONFIDENTIAL – PROPRIETARY INFORMATION

Drug Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	INC Research Pharmacovigilance & Drug Safety Fax: [redacted]
Issue Date:	29 Sep 2016
Date of Amendment 1:	7 Jun 2017
Version No.:	2.0

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: REXULTI, Brexpiprazole (OPC-34712)	Protocol No.: 331-201-00061 IND No.: 117,549
Protocol Title:	A Phase 2, Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial of Brexpiprazole (1 - 3 mg/day) as Monotherapy or as Combination Therapy in the Treatment of Adults with Post-traumatic Stress Disorder
Clinical Phase:	2
Treatment Indication:	Post-traumatic stress disorder (PTSD)
Objective(s):	Primary: To evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with Zoloft (sertraline) in adult subjects with PTSD. Secondary: To evaluate the safety and tolerability of brexpiprazole 1 to 3 mg/day as monotherapy or as combination treatment with Zoloft (sertraline) in adult subjects with PTSD.
Trial Design:	This is a phase 2, randomized, double-blind, placebo- and active-controlled 4-arm trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (1 - 3 mg/day) as monotherapy or as combination therapy with Zoloft (sertraline) in adult subjects with PTSD. The trial will be organized as follows: *Screening Phase:* The screening period will be up to 14 days and will begin when consent has been obtained. Additional extension(s) of up to 14 additional days can be requested from the medical monitor, if needed to meet eligibility requirements. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to washout prohibited concomitant pharmacotherapy, if applicable. An eSource method will be used to obtain an identification (ID) number for each subject with documented consent. Subjects will be between 18 and 65 years of age, inclusive, at the time of screening and will have a diagnosis of PTSD as defined by *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria. All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the

	protocol-specified washout periods. *Treatment Phase:* Subjects will be enrolled into a 12-week double-blind treatment period and randomized in a 1:1:1:1 ratio to one of the following double-blind treatment regimens: • brexpiprazole monotherapy • brexpiprazole and Zoloft (sertraline) combination therapy • Zoloft (sertraline) monotherapy • placebo Subjects will attend visits at Baseline (Day 0) and Weeks 1, 2, 3, 4, 6, 8, 10, and 12 during the treatment phase. *Follow-up:* If any subject discontinues the trial early, every effort should be made to complete the Week 12/early termination (ET) evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or clinic visit, 14 (+ 2) days after the last dose of investigational medicinal product (IMP). Any subject who withdraws because of a serious adverse event (SAE) should be seen in the clinic, if possible.
Subject Population:	The trial population will include male and female outpatients between 18 and 65 years of age at the time of consent, inclusive, with a DSM-5 diagnosis of PTSD.
Inclusion/Exclusion Criteria:	Key Inclusion Criteria: 1) Subjects who are able to complete the consent process and/or consent obtained from a legally acceptable representative (as required by institutional review board [IRB]/independent ethics committee [IEC]) prior to the initiation of any protocol-required procedures. 2) Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet/capsule ingestion, and discontinuation of prohibited concomitant medication; to read and understand the written word in order to complete subject-reported outcomes measures; and to be reliably rated on assessment scales. 3) Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent.

4) Subjects who have PTSD, diagnosed according to DSM-5, and confirmed by the Mini International Neuropsychiatric Interview (MINI).
5) The subject has a Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score ≥ 33 at Screening and Baseline (Day 0) Visits.
6) Onset of symptoms meeting the DSM-5 criteria for PTSD symptoms for a minimum of 6 months prior to screening.
7) Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

Key Exclusion Criteria:

1) Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. Males who do not agree to abstain from sperm donation during the trial and for 30 days after the last dose of IMP.
2) Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3) Subjects who are receiving disability payments because of PTSD or any other psychiatric disorder; unless the disability payments will not be impacted by potential improvements demonstrated in the trial, OR the subject is engaged in compensation litigation or other processes whereby personal gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorder.
4) The index traumatic event that led to development of PTSD took place >15 years before screening.
5) The index traumatic event occurred before age 16.
6) Subjects with PTSD who, in the investigator's opinion, are considered resistant/refractory to psychotropic treatment by history.
7) Subjects who are currently receiving Zoloft (sertraline)

with adequate dose and duration (> 50 mg/day for a minimum of 8 weeks).

8) Subjects who have had initiation of, or a change in, psychotherapy, eye-movement desensitization and reprocessing (EMDR) therapy or any other intervention for the treatment of PTSD symptoms within 28 days prior to the Screening Visit or it is anticipated that the subject will have a change in psychotherapy, EMDR therapy, or in any other intervention during the trial.
9) Subjects who meet the DSM-5 criteria for a current Major Depressive Episode (ie, currently symptomatic).
10) Subjects who have current or recent history (within 6 months prior to the Screening Visit) of an anxiety disorder that has been the primary focus of psychiatric treatment including: generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive, and other related disorders.
11) Subjects who have a DSM-5 diagnosis of delirium, major neurocognitive, or other cognitive disorder; schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or II disorder, or bipolar disorder not otherwise specified; eating disorder (including anorexia nervosa or bulimia); or borderline or antisocial personality disorders, or intellectual disability.
12) Subjects who have a current diagnosis or history of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) 120 days prior to the Screening Visit.
13) Subjects who have a positive urine drug screen that, in the judgment of the investigator with concurrence of the medical monitor, could compromise the subject's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results.
14) Subjects who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) or other neurological disorders or systemic medical diseases where the traumatic brain injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact patient safety, in the investigator's opinion.
15) Subjects who have experienced a traumatic event within 3 months of screening.

16) Subjects with a significant risk of committing suicide based on history, mental status examination, investigator's judgment, or C-SSRS answer of "yes" to question 4 or 5 (current or within the last 90 days).

17) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days prior to the Baseline [Day 0] Visit).

18) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevated to > 2 × the upper limit of normal [ULN]), or bariatric surgeries that may cause malabsorption. Medical conditions that are minor or well‑controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.

19) Subjects with insulin-dependent diabetes mellitus (IDDM) (ie, any subjects using insulin) are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:

- Glycosylated hemoglobin (HbA1c) < 7.0%, AND
- Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the non‑fasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, AND
- Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to

screening, AND

- Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND
- Subject's diabetes is not newly diagnosed during screening for the trial.

20) Subjects with uncontrolled hypertension (diastolic blood pressure [DBP] > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure (SBP) and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms.

21) Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile seizure, post traumatic, or alcohol withdrawal.

22) Subjects with abnormal laboratory tests results, vital signs results, or electrocardiogram (ECG) findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the subject or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial:

- Platelets ≤ 75000/mm^3
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute ≤ 1000/mm^3
- AST > 2 × ULN
- ALT > 2 × ULN
- Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
- Creatinine ≥ 2 mg/dL
- QT interval as corrected by Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing

23) Subjects who would be likely to require prohibited concomitant therapy during the trial.

	24) Subjects who received brexpiprazole in any prior clinical trial or currently taking commercially available brexpiprazole (Rexulti®). 25) Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome. 26) Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications. 27) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial. 28) Subjects who participated in a clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year. 29) Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.
Trial Site(s):	It is planned that approximately 610 subjects will be screened to enroll 332 subjects at approximately 45 trial sites in the United States (US).
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	During the double-blind treatment phase, subjects will receive IMP, consisting of brexpiprazole, brexpiprazole + Zoloft (sertraline), Zoloft (sertraline), or placebo depending on the subject's treatment assignment. All doses of IMP should be taken together at the same time each day, if possible. All doses of IMP can be taken without regard to meals. If tolerability issues arise, the timing of administration of the IMP may be adjusted at the investigator's discretion in order to achieve optimum tolerability and compliance.

Trial Assessments:	Efficacy: CAPS-5, Symptoms of Trauma Scale (SOTS), Clinical Global Impression - Severity (CGI-S), PTSD Checklist for DSM-5 (PCL-5), Hospital Anxiety and Depression Scale (HADS) and a wearable device. Pharmacokinetic (PK): A PK sample will be collected at Week 6 and Week 12 at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling. Safety: AE reporting, clinical laboratory tests, ECGs, vital signs, physical examination, body weight, height, waist circumference, Simpson-Angus Scale (SAS) total score, Abnormal Involuntary Movement Scale (AIMS) Movement Rating Score, and Barnes Akathisia Rating Scale (BARS) Global Score, and C-SSRS. Screening/Other: MINI, Life Events Checklist for DSM-5 (LEC-5), OSU TBI-ID, and Emory Treatment Resistance Interview for PTSD (E-TRIP) will be collected at screening. A pharmacogenomics sample to assess the cytochrome P450 (CYP) 2D6 metabolism status will also be collected at Week 6.

Criteria for Evaluation:	**Primary Endpoint:** Change from baseline in the CAPS-5 total score. **Other Endpoints:** Other efficacy endpoints are as follows: • Change from baseline in SOTS score • Change from baseline in CGI-S score • Change from baseline in PCL-5 score • Change from baseline in HADS score • Sleep related endpoints **Safety Endpoints:** Standard safety variables will include AEs, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], HbA1c, and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference will also be measured. Extrapyramidal symptoms (EPS) will be evaluated by calculating mean change from baseline in SAS total score, AIMS Movement Rating Score, and BARS Global Score. The C-SSRS will be used to assess and classify reported suicidal behavior. By-subject listings of physical examination findings will be reviewed as a further assessment of safety.

Statistical Methods:	Complete details of the planned statistical analysis will be presented in the unblinded addendum to this protocol and in the statistical analysis plan (SAP). Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation (SD). Tabulations of frequency distributions will be provided for categorical variables. The change from baseline in CAPS-5 total score will be analyzed using a mixed-effect model repeated measures (MMRM) methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial center, type of trauma, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CAPS-5 total score by visit week as a covariate. Other continuous efficacy endpoints will also be analyzed using MMRM methodology. Complete model details will be specified in the SAP.
Trial Duration:	The duration of this trial for an individual subject who completes the trial without ET is approximately 16 weeks. This is inclusive of a 14-day screening period, a 12-week double-blind treatment period, and a safety follow-up period 14 (+2) days after the dose of IMP.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	Serotonin
ADHD	Attention-deficit hyperactivity disorder
ADT	Antidepressive therapy
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-HCV	Antibodies to hepatitis C virus
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BUN	Blood urea nitrogen
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CGI-S	Clinical Global Impression - Severity
CPK	Creatine phosphokinase
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DA	Dopamine
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
EMDR	Eye-movement desensitization and reprocessing
EPS	Extrapyramidal symptoms
ET	Early termination
EU	European Union
FBR	Future biospecimen research
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HADS	Hospital Anxiety and Depression Scale
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification

IDDM	Insulin-dependent diabetes mellitus
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LEC-5	Life Events Checklist for DSM-5
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effect model repeated measure
MTD	Maximum tolerated dose
OC	Observed case
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
PCL-5	PTSD Checklist for DSM-5
PET	Positron-emission tomography
PK	Pharmacokinetic
PQC	Product quality complaint
PTSD	Post-traumatic stress disorder
QD	Once-daily
QTcF	QT interval as corrected by Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SBP	Systolic blood pressure
SD	Standard deviation
SOTS	Symptoms of Trauma Scale
SSRI	Selective serotonin reuptake inhibitor
T_4	Free thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
US or USA	United States or United States of America
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

1 Introduction

Post-traumatic stress disorder (PTSD) is a prevalent, debilitating, and often chronic neuropsychiatric illness that may develop in a person who has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others. The person's response involves intense fear, helplessness, or horror. According to *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5), the diagnostic criteria for PTSD include a history of exposure to a traumatic event that meets specific stipulations and symptoms from each of 4 symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. The sixth criterion concerns duration of symptoms; the seventh assesses functioning; and, the eighth criterion clarifies symptoms as not attributable to a substance or co-occurring medical condition. The United States (US) National Comorbidity Survey Replication, found a PTSD lifetime prevalence of 6.8%, and a 12-month prevalence of 3.6%, with rates of 5.2% for women and 1.8% for men.[1,2]

The selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline are currently approved for the treatment of PTSD by the Food and Drug Administration (FDA) in the US. Response rates with SSRIs in PTSD are moderate, reaching approximately 60%.[3] Several clinical trials have been conducted with atypical antipsychotics in PTSD.[4]

Brexpiprazole (OPC-34712, OPC-331, and Lu AF41156) is a new chemical entity discovered by Otsuka that is being codeveloped by Otsuka and Lundbeck. Brexpiprazole is currently approved in the US for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and monotherapy treatment of schizophrenia. While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the serotonin (5-HT) and dopamine (DA) systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (K_i: 0.1 - 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ with affinity in the same subnanomolar K_i range (K_i: 0.2 - 0.6 nM). The 5-HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole

may correlate with antipsychotic and antidepressant efficacy, reduced impulsive behavior, and cognitive improvement.[5]

1.1 Nonclinical Data

A complete description of the available efficacy and safety pharmacology data from nonclinical studies, including pharmacokinetic (PK) and toxicology studies in different animal species can be found in the current Investigator's Brochure (IB) for more detailed information.[5]

1.2 Clinical Data

Currently, brexpiprazole is approved in the US for use in adult patients as an adjunctive therapy to antidepressants for the treatment of MDD and monotherapy treatment of schizophrenia. Additionally, the current clinical development program is designed to show safety and efficacy of brexpiprazole for the treatment of the following indications: adjunctive treatment of adult attention-deficit hyperactivity disorder (ADHD; coadministered with marketed stimulant therapy); treatment of agitation associated with dementia of the Alzheimer's type; and treatment of adult PTSD.[5]

As of 17 Apr 2016, the brexpiprazole clinical development program consisted of a total of 65 clinical trials conducted in North America, Latin America, Europe, and Asia (53 completed and 12 ongoing). This includes 59 trials conducted under US Investigational New Drug Applications (INDs) (47 completed and 12 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of ADHD, agitation associated with dementia of the Alzheimer's type, or PTSD; and 6 non-US IND trials completed in either Korea or Japan conducted in healthy subjects and subjects with schizophrenia.[5]

Please refer to the IB for more detailed information.[5]

1.3 Known and Potential Risks and Benefits

Phase 1 data indicated that brexpiprazole had good safety and tolerability when administered to healthy volunteers at single doses of 0.2 to 6 mg and at a repeated dose of 2 mg/day. Data from completed repeated dosing trials in the US indicate that brexpiprazole had good tolerability when administered to patients with schizophrenia or schizoaffective disorder at doses of up to 12 mg/day; when administered to patients with MDD at doses of up to 4 mg/day in combination with a marketed antidepressant; and

when administered to patients with ADHD at doses of up to 4 mg/day in combination with a marketed stimulant.[5]

Please refer to the current IB for a summary of available nonclinical and clinical safety data.[5]

Zoloft (sertraline) is indicated for the treatment of PTSD at dose of 50-200 mg/day. The most frequently reported treatment-emergent adverse events (TEAEs) (incidence of at least 5% for Zoloft and at least twice that for placebo) in patients with PTSD were ejaculation failure, fatigue, anorexia, libido decreased, and tremor.[6]

2 Trial Rationale and Objectives

2.1 Trial Rationale

Two pharmacologic therapies (paroxetine and sertraline) are currently approved for treatment for PTSD by the US FDA, but only moderate clinical success has been demonstrated. Most clinical guidelines recommend paroxetine and sertraline as the first-line pharmacological intervention for PTSD. However, the response rates to paroxetine and sertraline in PTSD are moderate and few patients achieve remission. Consequently, there is a need for additional treatment options.

Only 1 trial has been conducted with brexpiprazole in subjects with PTSD. Trial 14865A was a phase 3 trial for adjunctive treatment with brexpiprazole in subjects with PTSD who had an inadequate response to treatment with paroxetine or sertraline. Trial 14865A was terminated early due to challenges with patient eligibility; the decision to terminate was not based on any safety concerns.

Trial 331-201-00061 aims to evaluate whether brexpiprazole as monotherapy or combination treatment is more effective than Zoloft (sertraline) alone or placebo in relieving PTSD symptoms in non-newly diagnosed subjects and to confirm that it is safe and well tolerated.

2.2 Dosing Rationale

The doses of brexpiprazole to be used in Trial 331-201-00061 have been determined based on results of previously completed clinical phase 1 pharmacology trials, a positron-emission tomography (PET) trial in healthy subjects, and a phase 3 trial in PTSD.

The clinical pharmacology program consists of multiple ascending dose monotherapy trials in healthy subjects and subjects with schizophrenia as well as adjunctive trials in subjects with MDD, and ADHD. The maximum tolerated dose (MTD) for healthy subjects has been determined to be 6 mg after single-dose administration and 2 mg after once-daily (QD), multiple-dose (14 days) administration. The MTD of brexpiprazole in subjects with schizophrenia, MDD, or ADHD has not been established. The following doses of brexpiprazole have been tolerated in completed phase 1 clinical pharmacology trials:

- 12 mg/day after QD, multiple-dose administration to adult subjects with schizophrenia or schizoaffective disorder,
- 4 mg/day after QD, multiple-dose administration to adult subjects with MDD when coadministered with marketed antidepressive therapy (ADT),
- 3 mg/day after QD, multiple-dose administration to elderly subjects (70 - 85 years of age) with MDD when coadministered with marketed ADT, and
- 4 mg/day after QD, multiple-dose administration to adult subjects with ADHD when coadministered with marketed stimulant therapy.

Results from the PET trial in healthy subjects (Trial 331-07-202) predicted steady state dopamine D_2 and D_3 receptor occupancies of at least 80% to 90% at brexpiprazole doses of 1 to 2 mg/day and higher (79.3% predicted occupancy at brexpiprazole 1 mg/day, 88.8% at brexpiprazole 2 mg/day, and 95.1% at brexpiprazole 4 mg/day).

Results from subjects with PTSD (Trial 14865A) showed that brexpipazole doses of 1 to 3 mg/day were well tolerated.

Therefore, based in the collective safety, tolerability, and receptor occupancy data, a dose range of 1 to 3 mg/day brexpiprazole was chosen for evaluation in Trial 331-201-00061.

Zoloft (sertraline) is indicated for the treatment of PTSD at doses of 50-200 mg/day.

2.3 Trial Objectives

The primary objective is to evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with Zoloft (sertraline) in adult subjects with PTSD.

The secondary objective is to evaluate the safety and tolerability of brexpiprazole 1 to 3 mg/day as monotherapy or as combination treatment with Zoloft (sertraline) in adult subjects with PTSD.

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3 Trial Design

3.1 Type/Design of Trial

This is a phase 2, randomized, double-blind, placebo- and active-controlled, 4-arm trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (1 - 3 mg/day) as monotherapy or as combination therapy with Zoloft (sertraline) in adult subjects with PTSD. See Figure 3.1-1 for a schematic of the trial design.

The trial will be organized as follows:

Screening Phase: The screening period will be up to 14 days and will begin when consent has been obtained. Additional extension(s) of up to 14 additional days can be requested from the medical monitor, if needed to meet eligibility requirements. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to washout prohibited concomitant pharmacotherapy, if applicable. An eSource method will be used to obtain an identification (ID) number for each subject with documented consent. Subjects will be between 18 and 65 years of age, inclusive, at the time of screening and will have a diagnosis of PTSD as defined by DSM-5 criteria.

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods.

Treatment Phase: Subjects will be enrolled into a 12-week double-blind treatment period and randomized in a 1:1:1:1 ratio to one of the following double-blind treatment regimens:

- brexpiprazole monotherapy
- brexpiprazole and Zoloft (sertraline) combination therapy
- Zoloft (sertraline) monotherapy
- placebo

Subjects will attend visits at Baseline (Day 0) and Weeks 1, 2, 3, 4, 6, 8, 10, and 12 during the treatment phase.

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the Week 12/early termination (ET) evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via

telephone or clinic visit, 14 (+ 2) days after the last dose of investigational medicinal product (IMP). Any subject who withdraws because of a serious adverse event (SAE) should be seen in the clinic, if possible.

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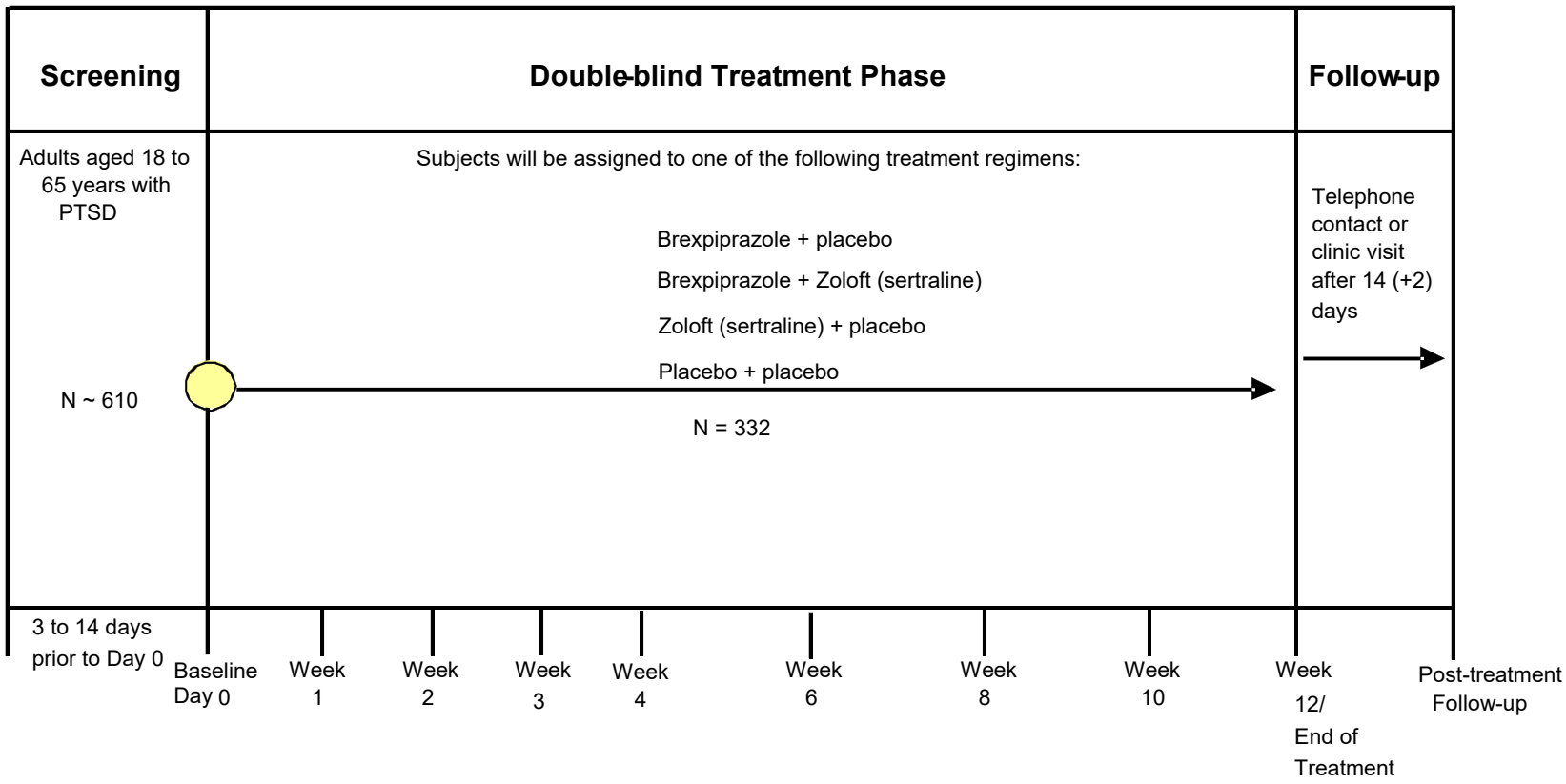

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

During the first 3 weeks of the trial, subjects will be titrated according to the blinded titration schedule, based on the treatment group to which they will be randomized. Per this schedule, at Week 3, subjects will receive:

1. Brexpiprazole monotherapy 2 mg/day; or
2. Brexpiprazole 2 mg/day + Zoloft (sertraline) 150 mg/day; or
3. Zoloft (sertraline) monotherapy 150 mg/day; or
4. Placebo.

No dose adjustments are allowed during the 3 week titration period, thus any subject unable to tolerate the assigned dose of IMP during the titration period must be withdrawn from the trial.

Once the subject takes the first dose following the forced titration period, the dose of IMP can be adjusted to optimize efficacy and safety/tolerability according to the following rules:

- Dose increases can occur only at the Week 4 visit.
- Dose decreases can occur at scheduled or unscheduled visits starting after the first dose following Week 3 and are not allowed after the Week 6 visit.
- Dose may be maintained, decreased (if not decreased already) or increased at the Week 4 visit. No further dose increases are permitted after Week 4.
- Dose decreases will be allowed between Week 3 (following the first post-visit dose as above) and Week 6, if there are tolerability issues.
- Dose must be maintained for the remainder of the treatment period after Week 6.
- If subjects are unable to maintain the Week 6 dose due to tolerability issues, the subject must be withdrawn from the trial.

All doses of IMP should be taken together at the same time each day, if possible. All doses of IMP can be taken without regard to meals. If tolerability issues arise, the timing of administration of the IMP may be adjusted at the investigator's discretion in order to achieve optimum tolerability and compliance.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

It is planned that approximately 610 subjects will be screened to enroll 332 subjects at approximately 45 trial sites in the US.

The trial population will include male and female outpatients between 18 and 65 years of age at the time of consent, inclusive, with a DSM-5 diagnosis of PTSD.

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique subject ID number upon completion of the consent process based on sequential enrollment in the trial.

3.4 Eligibility Criteria

3.4.1 Electronic Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The informed consent form (ICF) will be approved by the same institutional review board (IRB)/independent ethics committee (IEC) that approves this protocol.

Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[7] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site‑specific ICF used in the trial before submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for the trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial participants will be provided with controlled access to the electronic informed consent application by site personnel. When the site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign the electronic ICF application and an electronic date and time stamp will be applied to the signature. The participant will be given a printed copy of the consent form. Any other parties required by the IRB/IEC (site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Subjects who are able to complete the consent process and/or consent obtained from a legally acceptable representative (as required by IRB/IEC) prior to the initiation of any protocol-required procedures.
2.	Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet/capsule ingestion, and discontinuation of prohibited concomitant medication; to read and understand the written word in order to complete subject-reported outcomes measures; and to be reliably rated on assessment scales.
3.	Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent.
4.	Subjects who have PTSD, diagnosed according to DSM-5, and confirmed by the MINI.
5.	The subject has a CAPS-5 total score ≥ 33 at Screening and Baseline (Day 0) Visits.
6.	Onset of symptoms meeting the DSM-5 criteria for PTSD symptoms for a minimum of 6 months prior to screening.
7.	Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; MINI = Mini International Neuropsychiatric Interview.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

Sex and Reproductive Status	
1.	Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. Males who do not agree to abstain from sperm donation during the trial and for 30 days after the last dose of IMP.
2.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
Target Disease	
3.	Subjects who are receiving disability payments because of PTSD or any other psychiatric disorder; unless the disability payments will not be impacted by potential improvements demonstrated in the trial, OR the subject is engaged in compensation litigation or other processes whereby personal gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorder.
4.	The index traumatic event that led to development of PTSD took place > 15 years before screening.
5.	The index traumatic event occurred before age 16.
6.	Subjects with PTSD who, in the investigator's opinion, are considered resistant/refractory to psychotropic treatment by history.
7.	Subjects who are currently receiving Zoloft (sertraline) with adequate dose and duration (> 50 mg/day for a minimum of 8 weeks).
8.	Subjects who have had initiation of, or a change in, psychotherapy, EMDR therapy or any other intervention for the treatment of PTSD symptoms within 28 days prior to the Screening Visit or it is anticipated that the subject will have a change in psychotherapy, EMDR therapy, or in any other intervention during the trial.
9.	Subjects who meet the DSM-5 criteria for a current Major Depressive Episode (ie, currently symptomatic).
10.	Subjects who have current or recent history (within 6 months prior to the Screening Visit) of an anxiety disorder that has been the primary focus of psychiatric treatment including: generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive, and other related disorders.
11.	Subjects who have a DSM-5 diagnosis of delirium, major neurocognitive, or other cognitive disorder; schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or II disorder, or bipolar disorder not otherwise specified; eating disorder (including anorexia nervosa or bulimia); or borderline or antisocial personality disorders, or intellectual disability.
12.	Subjects who have a current diagnosis or history of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) 120 days prior to the Screening Visit.
13.	Subjects who have a positive urine drug screen that, in the judgment of the investigator with concurrence of the medical monitor, could compromise the subject's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results.
14.	Subjects who have a history of moderate or severe head trauma as assessed by the OSU TBI-ID or other neurological disorders or systemic medical diseases where the traumatic brain injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact patient safety, in the investigator's opinion.
15.	Subjects who have experienced a traumatic event within 3 months of screening.

Table 3.4.3-1 Exclusion Criteria	
Medical History and Concurrent Diseases	
16.	Subjects with a significant risk of committing suicide based on history, mental status examination, investigator's judgment, or C-SSRS answer of "yes" to question 4 or 5 (current or within the last 90 days).
17.	Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days prior to the Baseline [Day 0] Visit).
18.	Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as ischemic heart disease, myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and AST or ALT elevated to > 2 × ULN), or bariatric surgeries that may cause malabsorption. Medical conditions that are minor or well‑controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a corresponding high BMI (BMI ≥ 40 kg/m^2), need to be reviewed and discussed with the medical monitor.
19.	Subjects with IDDM (ie, any subjects using insulin) are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria: • HbA1c < 7.0%, AND • Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the non‑fasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, AND • Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, AND • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND • Subject's diabetes is not newly diagnosed during screening for the trial.
20.	Subjects with uncontrolled hypertension (DBP > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms. NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above.
21	Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile seizure, post traumatic, or alcohol withdrawal.

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Table 3.4.3-1 Exclusion Criteria	
Physical and Laboratory Results	
22.	Subjects with abnormal laboratory tests results, vital signs results, or ECG findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the subject or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Criteria are provided in Appendix 2, Appendix 3, and Appendix 4 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: • Platelets ≤ 75000/mm^3 • Hemoglobin ≤ 9 g/dL • Neutrophils, absolute ≤ 1000/mm^3 • AST > 2 × ULN • ALT > 2 × ULN • CPK > 3 × ULN, unless discussed with and approved by the medical monitor • Creatinine ≥ 2 mg/dL • QTcF ≥ 450 msec in men and ≥ 470 msec in women (see Section 3.7.3.4 for further details), unless due to ventricular pacing Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the subject must be excluded.
Disallowed Recent and Concomitant Medication	
23.	Subjects who would be likely to require prohibited concomitant therapy during the trial (see Table 4.1-2).
24.	Subjects who received brexpiprazole in any prior clinical trial or currently taking commercially available brexpiprazole (Rexulti®).
Allergies and Adverse Drug Reactions	
25.	Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome.
26.	Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.
Other	
27.	Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
28.	Subjects who participated in a clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year.
29.	Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CPK = creatine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; ECG = electrocardiogram; EMDR = eye-movement desensitization and reprocessing; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; OSU TBI-ID = Ohio State University Traumatic Brain Injury Identification Method; QTcF = QT interval as corrected by Fridericia's formula; SBP = systolic blood pressure; ULN = upper limit of normal.

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months with no menses without an alternative medical cause.

Subjects must agree to restrictions to medications and lifestyle as described in Section 4.

Subjects with a positive blood alcohol screen should be reassessed for alcohol abuse and dependence before consultation with medical monitor about approval for inclusion. Subjects with a positive drug screen that, in the judgment of the investigator with concurrence of the medical monitor, could compromise the subject's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results. Detectable levels of marijuana, barbiturates, stimulants, or opiates in the drug screen are not exclusionary if:

- In the investigator's documented opinion, the subject does not meet DSM-5 criteria for substance abuse or dependence, and
- In the investigator's documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, and
- The medical monitor's approval is obtained prior to the Baseline (Day 0) Visit.

Screen failures due to exclusionary criteria may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, additional 14-day extension(s) of screening may be requested from the medical monitor. Any extension should be requested prior to the expiration of the previous extension or screening period, as applicable. If no extension is granted, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. Subjects may be rescreened twice for this trial.

3.5 Endpoints

3.5.1 Primary Efficacy Endpoint

Change from baseline in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score.

3.5.2 Other Efficacy Endpoints

Other efficacy endpoints are as follows:

- Change from baseline in Symptoms of Trauma Scale (SOTS) score
- Change from baseline in Clinical Global Impression - Severity (CGI-S) score
- Change from baseline in PTSD Checklist for DSM-5 (PCL-5) score
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) score
- Sleep related endpoints

3.5.3 Safety Endpoints

Standard safety variables will include adverse events (AEs), clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], glycosylated hemoglobin [HbA1c], and urinalysis), physical examinations, vital sign measurements, and electrocardiograms (ECGs). Body weight, height, and waist circumference will also be measured.

Extrapyramidal symptoms (EPS) will be evaluated by calculating mean change from baseline in Simpson-Angus Scale (SAS) total score, Abnormal Involuntary Movement Scale (AIMS) Movement Rating Score, and Barnes Akathisia Rating Scale (BARS) Global Score. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess and classify reported suicidal behavior. By-subject listings of physical examination findings will be reviewed as a further assessment of safety.

3.5.4 Pharmacokinetic/Pharmacogenomic Variables

A PK sample will be collected at Week 6 and Week 12 at the same time of collection of clinical labs. Samples will be analyzed for brexpiprazole and its major metabolite, DM-3411, concentrations using a high-performance liquid chromatography with tandem mass spectrometry method.

A pharmacogenomics sample to assess the cytochrome P450 (CYP)2D6 metabolism status will also be collected at Week 6. Time of last 3 doses will be recorded at the time of PK sampling.

3.6 Measures to Minimize/Avoid Bias

During the entire trial, treatment will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment at any given visit.

Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Biometrics Department. The randomization will be stratified by trial site and type of trauma (combat related Yes/No). Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the IRT, and reporting SAEs to regulatory agencies.

3.7 Trial Procedures

This is a phase 2, randomized, double-blind, placebo- and active-controlled, 4-arm trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (1 - 3 mg/day) as monotherapy or as combination therapy with Zoloft (sertraline) in adult subjects with PTSD. The trial is a continuous, 12-week, double-blind treatment period with a 14-day follow-up (Figure 3.1-1).

Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
ENTRANCE CRITERIA											
Informed Consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical history	X										
Psychiatric history including PTSD history	X										
MINI	X										
PTSD treatments: pharmacological and non-pharmacological and E-TRIP	X										
Prior medication washout[d]	X										
LEC-5	X										
OSU TBI-ID	X										
HIV, HBsAg, and anti-HCV	X										
Review of birth control methods	X	X	X	X	X	X	X	X	X	X	X
EFFICACY											
CAPS-5[e]	X	X	X		X		X		X	X	
SOTS		X				X				X	
CGI-S		X	X	X	X	X	X	X	X	X	
PCL-5		X	X		X		X		X	X	
HADS		X	X		X		X		X	X	
Wearable device[f]		X	X	X	X	X	X	X	X	X	
SAFETY											
Assess need for double-blind IMP dose modification						X	X				

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
Physical examination[g]	X									X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[i]	X	X								X	
Clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], urinalysis), TSH[j]	X	X[k]					X			X	
HbA1c	X									X	
Insulin	X	X[k]								X	
Urine drug screen/blood alcohol[l]	X									X	
Urine pregnancy test[m]	X	X				X		X		X	
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	
SAS		X		X			X			X	
AIMS		X		X			X			X	
BARS		X		X			X			X	
Adverse events[o]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[p]		X	X	X	X	X	X	X	X	X	X
OTHER											
Drug dispensing[q]		X	X	X	X	X	X	X	X		
Drug accountability			X	X	X	X	X	X	X	X	
Pharmacokinetic and Pharmacogenomic Sampling											
PK sample[r]							X			X	
Pharmacogenomic sample[s]							X				

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
FBR sample[t]							X				

anti-HCV = antibodies to hepatitis C virus; E-TRIP = Emory Treatment Resistance Interview for PTSD; FBR = future biospecimen research; HBsAg = hepatitis B surface antigen; LEC-5 = Life Events Checklist for DSM-5; TSH = thyroid-stimulating hormone.

[a]Screening begins upon completion of the consent process. Although the screening period takes place between Day −14 and Day −3 prior to enrollment, subjects will participate in screening activities for a minimum of 3 days. It is requested to complete screening as quickly as possible. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, additional 14-day extension(s) of screening may be requested from the medical monitor. Any extension should be requested prior to the expiration of the previous extension or screening period, as applicable.

[b]If a subject discontinues early, every effort should be made to complete the "End of Week 12/ET" evaluations as soon as possible and whenever possible prior to starting any new medication or treatment.

[c]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety.

[d]Washout of prohibited medications begins after completion of the consent process and must comply with the required washout periods in Section 4.1.

[e]The CAPS-5 Past Month version will be completed for all subjects at screening to determine eligibility and the CAPS-5 Past Week version will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial. The CAPS-5 Past Week version will also be completed at all visits after the Baseline (Day 0) Visit when the assessment is scheduled for collection.

[f]The wearable device will be put on the subject's nondominant wrist, whenever possible, at the Baseline (Day 0) Visit and worn daily until Week12/ET. The trial site will download Actigraphy data during each subject visit.

[g]To include measurement of height (at screening only) and waist circumference.

[h]Vital sign measurements include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine and standing after the subject has been in each position for at least 3 minutes.

[i]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated in triplicate to confirm the finding(s) before excluding the subject from the trial (see Section 3.7.3.4). A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis.

[j]Blood samples for clinical laboratory tests should be drawn after a minimum 8-hour fast at the Baseline (Day 0) Visit and should be drawn after a minimum 8-hour fast at screening, if possible. If blood draws are not part of the site's SOP, the subject should not be asked to fast for the study prior to signing the ICF.

[k]If a fasting blood sample was not obtained at the Screening Visit and if more than 10 days have elapsed since the Screening Visit, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], TSH with reflex to T_4 if the result for TSH is abnormal, and urinalysis) need to be repeated at the Baseline (Day 0) Visit.

[l]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator (Section 4.2.2.2). See Section 3.4.3 for exclusions based on urine drug screen and blood alcohol tests at screening and baseline requirements based on urine drug screen and blood alcohol results.

[m]For women of childbearing potential only (WOCBP). All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[n]The "Baseline/Screening" C-SSRS form will be completed for all subjects at screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at all visits after the Baseline (Day 0) Visit.

[o]Adverse events will be recorded starting after the subject completes the consent process.

[p]All prescription and non-prescription medications taken during the trial will be recorded. Details of prohibited medications are provided in Section 4.

[q]The subject will be instructed to take their first dose the day after the Baseline (Day 0) Visit (see Section 3.7.1.2).

[r]A PK sample will be collected at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling.

[s]A pharmacogenomics sample to assess the CYP2D6 metabolism status will also be collected.

[t]FBR sample will be collected if subject consent is received and if allowed by IRB/IEC (see Section 3.7.5).

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3.7.1 Schedule of Assessments

3.7.1.1 Screening

The screening period begins after consent has been obtained. Although the screening period takes place between Day −14 and Day −3, subjects will participate in screening activities for a minimum of 3 days. It is requested to complete screening as quickly as possible. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, additional 14-day extension(s) of screening may be requested from the medical monitor. Any extension should be requested prior to the expiration of the previous extension or screening period, as applicable. After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing eSource. Completion of screening activities may require more than one visit; however, only the initial visit will be registered in the eSource. Screening evaluations will include the following:

- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Demographic data will be recorded.
- A general clinical evaluation will be performed, including concurrent medical conditions, medical history over the past 2 years, and medical history beyond 2 years which is considered to be clinically relevant per the investigator's judgment.
- Psychiatric history will be recorded, including the DSM-5 diagnosis of PTSD that will be made by an adequately trained and experienced clinician and will be confirmed by the administration of the Mini International Neuropsychiatric Interview (MINI).
- Medications (including those that were taken within 30 days preceding the first dose of IMP) will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited/restricted medications are provided in Table 4.1-2.
- All pharmacological and non-pharmacological treatments for PTSD using the Emory Treatment Resistance Interview for PTSD (E-TRIP) assessment.
- Washout from prohibited concomitant medications will begin, if applicable, (see Table 4.1-1).
- Subject will complete the Life Events Checklist for DSM-5 (LEC-5) assessment. The LEC-5 assessment will be reviewed for completeness by the same qualified and certified rater administering the CAPS-5.
- A qualified and certified rater will administer the CAPS-5. Subjects with CAPS-5 total score < 33 at screening or baseline are excluded from the trial.
- The investigator (or qualified designee) will administer the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID).

- A complete physical examination (including height and waist circumference) will be performed.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes. See Table 3.4.3-1 for exclusions based on outcome of screening vital sign measurements.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. See Table 3.4.3-1 for exclusions based on ECG results.
- Blood samples for clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], HbA1c, thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T_4] if the result for TSH is abnormal, insulin, and urinalysis) should be drawn after a minimum 8-hour fast at screening. See Table 3.4.3-1 for exclusions based on outcome of screening clinical laboratory tests.
- Blood samples will be drawn for human immunodeficiency virus (HIV) serology and the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV).
- Samples will be obtained for blood alcohol testing. See Section 3.4.3 for detail of subjects with a positive blood alcohol test.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Section 3.4.3 for exclusions based on outcome of screening urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all women of childbearing potential (WOCBP). All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- The investigator (or qualified designee) will complete the “Baseline/Screening” C-SSRS form to exclude subjects with a significant risk of suicidal behavior (see Table 3.4.3-1).
- Adverse events will be recorded beginning with the completion of the consent process.

3.7.1.2 Baseline (Day 0) Visit

If the subject is found to be eligible for the trial during the screening period, the subject will attend a baseline visit during which the following procedures will be performed:

- An assessment of all inclusion and exclusion criteria will be made to determine the subject’s eligibility for the trial.
- A qualified and certified rater will administer the CAPS-5. Whenever possible, it is recommended that the CAPS-5 is conducted as the first assessment of the visit.
- The investigator (or qualified designee) will administer the CGI-S and SOTS.

- The subject will complete the HADS and PCL-5. Assessments will be reviewed for completeness by the investigator (or qualified designee).
- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes. See Table 3.4.3-1 for exclusions based on outcome of vital sign measurements.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. See Table 3.4.3-1 for exclusions based on ECG results.
- If a fasting blood sample was not obtained at the Screening Visit and if more than 10 days have elapsed since the Screening Visit, blood samples for clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], TSH with reflex to T_4 if the result for TSH is abnormal, insulin, and urinalysis) should be drawn after a minimum 8-hour fast at Baseline (Day 0) Visit.
- A urine pregnancy test will be performed for all WOCBP. All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- The assigned IMP will be dispensed to the subject. The subjects should be instructed to take their first dose the day after the Baseline (Day 0) Visit.
- The wearable device will be put on subject's nondominant wrist. The wearable device will be worn continuously throughout the double-blind treatment period.

3.7.1.3 Treatment Phase - Week 1

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- A qualified and certified rater will administer the CAPS-5. Whenever possible, it is recommended that the CAPS-5 is conducted as the first assessment of the visit.
- The investigator (or qualified designee) will administer the CGI-S.
- The subject will complete the HADS and PCL-5. Assessments will be reviewed for completeness by the investigator (or qualified designee).
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.

- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.4 Treatment Phase - Week 2

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- The investigator (or qualified designee) will administer the CGI-S.
- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.5 Treatment Phase - Week 3

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- A qualified and certified rater will administer the CAPS-5. Whenever possible, it is recommended that the CAPS-5 is conducted as the first assessment of the visit.
- The investigator (or qualified designee) will administer the CGI-S.
- The subject will complete the HADS and PCL-5. Assessments will be reviewed for completeness by the investigator (or qualified designee).
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the

following order: supine and standing after the subject has been in each position at least 3 minutes.

- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.6 Treatment Phase - Week 4

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- The investigator (or qualified designee) will administer the CGI-S and SOTS.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- All WOCBP will be given a urine pregnancy test. The result must be negative prior to dosing. All positive results must be confirmed by a serum pregnancy test.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- Trial personnel will assess need for double-blind IMP dose modification.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.7 Treatment Phase - Week 6

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- A qualified and certified rater will administer the CAPS-5. Whenever possible, it is recommended that the CAPS-5 is conducted as the first assessment of the visit.
- The investigator (or qualified designee) will administer the CGI-S.

- The subject will complete the HADS and PCL-5. Assessments will be reviewed for completeness by the investigator (or qualified designee).
- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- Blood samples for clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], TSH with reflex to T_4 if the result for TSH is abnormal, and urinalysis) should be drawn after a minimum of 8-hour fasting.
- A PK sample will be collected at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling.
- A pharmacogenomics sample to assess the CYP2D6 metabolism status will also be collected.
- A future biospecimen research (FBR) sample will be collected to explore and identify biomarkers if subject consent is received and if allowed by IRB/IEC.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- Trial personnel will assess need for double-blind IMP dose modification.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.8 Treatment Phase - Week 8

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- The investigator (or qualified designee) will administer the CGI-S.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- All WOCBP will be given a urine pregnancy test. The result must be negative prior to dosing. All positive results must be confirmed by a serum pregnancy test.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.

- Adverse events and concomitant medications will be recorded.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.9 Treatment Phase - Week 10

Visit is to occur within ± 2 days of the target visit date. The following procedures will be performed during the Treatment Phase visit:

- A qualified and certified rater will administer the CAPS-5. Whenever possible, it is recommended that the CAPS-5 is conducted as the first assessment of the visit.
- The investigator (or qualified designee) will administer the CGI-S.
- The subject will complete the HADS and PCL-5. Assessments will be reviewed for completeness by the investigator (or qualified designee).
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form to assure that the subject continues to qualify for the trial.
- Adverse events and concomitant medications will be recorded.
- The assigned IMP will be dispensed to the subject.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.

3.7.1.10 End of Week 12/Early Termination

The Week 12 Visit signifies the end of treatment for all subjects. Therefore, all subjects will undergo a complete evaluation at Week 12 (± 2 days).

In addition, Week 12 evaluations are to be completed for any subject withdrawn from the trial at any time (for any reason other than full withdrawal of consent). Every effort should be made to complete the Week 12/ET evaluations as soon as possible after discontinuation and whenever possible prior to starting any new medication or treatment. Trial personnel should make every attempt to complete all evaluations, particularly efficacy assessments (ie, CAPS-5, SOTS, CGI-S, PCL-5, and HADS), scheduled for the Week 12/ET visit as soon as possible and before administration of any new treatments.

Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes. Emphasis should be placed on obtaining information on treatment received and healthcare resources used subsequent to withdrawal from trial treatment.

The following activities and assessments will occur at Week 12 (or at the ET visit, if applicable):

- A qualified and certified rater will administer the CAPS-5. Whenever possible, it is recommended that the CAPS-5 is conducted as the first assessment of the visit.
- The investigator (or qualified designee) will administer the CGI-S and SOTS.
- The subject will complete the HADS and PCL-5. Assessments will be reviewed for completeness by the investigator (or qualified designee).
- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS.
- A complete physical examination (including waist circumference) will be performed. Repeat measurement of height is not required.
- Measurements of vital signs (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
- Blood samples for clinical laboratory tests (hematology, HbA1c, serum chemistry [including blinded prolactin], TSH with reflex to T_4 if the result for TSH is abnormal, insulin, and urinalysis) and blood alcohol testing should be drawn after a minimum 8-hour fast at Week 12/ET.
- A PK sample will be collected at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling.
- Urine will be collected for urinalysis and urine screen(s) for drugs of abuse.
- All WOCBP will be given a urine pregnancy test. All positive results must be confirmed by a serum pregnancy test.
- The investigator (or qualified designee) will complete the “Since Last Visit” C-SSRS form.
- Adverse events and concomitant medications will be recorded.
- Drug accountability will be performed.
- The wearable device will be taken off and the data will be downloaded to the computer, and the wearable device monitoring will be stopped.

3.7.1.11 Post-treatment Follow-up Period

Subjects will be contacted to monitor for safety events via telephone contact or clinic visit (investigator's discretion), 14 (+ 2) days after the last dose of IMP. Adverse events and concomitant medications will be recorded. This contact also applies to subjects withdrawn prematurely from the trial.

3.7.2 Efficacy Assessments

It is required that trained and experienced clinicians administer all rating scales. In addition, the raters must be certified for this trial to administer the CAPS-5. The number of raters within each trial center should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training, certification, and materials for rating will be provided by OPDC or designee.

3.7.2.1 Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The CAPS-5[8,9] is a clinician-rated, structured interview designed to assess PTSD diagnostic status and symptoms severity as defined by the DSM-5. This trial will use the CAPS-5 Past Month and CAPS-5 Past Week versions of the scale. The CAPS-5 comprises questions that target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS-5 administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization).

The CAPS-5 is scored by summing severity scores for the 20 DSM-5 PTSD symptoms. Similarly, CAPS-5 symptom cluster severity scores are calculated by summing the individual item severity scores for symptoms corresponding to a given DSM-5 cluster: Criterion B (items 1-5); Criterion C (items 6-7); Criterion D (items 8-14); and, Criterion E (items 15-20). A symptom cluster score may also be calculated for dissociation by summing items 29 and 30.

The CAPS-5 will be administered by a qualified and certified rater. It takes on average between 45 and 60 minutes to administer the CAPS-5. Samples of the CAPS-5 Past Month and CAPS-5 Past Week versions are provided in Appendix 5 and Appendix 6, respectively.

3.7.2.2 Symptoms of Trauma Scale (SOTS)

The SOTS[10] is a 12-item 7-point symptom severity rating scale designed to measure change. Ratings for each of the 12 symptoms can range from 1 = Absent to 7 = Extreme. Because the SOTS provides a means of rating of symptoms at 7 levels of severity (absent, minimal, mild, moderate, moderate severe, severe, and extreme), it can assess changes in trauma symptoms, which will become increasingly important as new interventions, both psychosocial and pharmacological, emerge. Ratings are based upon information obtained from a structured clinical interview, using both behavior observed during the 20 to 30 minute interview as well as the subject's report regarding functioning for the past week. A sample of the SOTS is provided in Appendix 7.

3.7.2.3 Clinical Global Impression - Severity (CGI-S)

The severity of illness for each subject will be rated using the CGI-S.[11] To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects. A sample of the CGI-S is provided in Appendix 8.

3.7.2.4 PTSD Checklist for DSM-5 (PCL-5)

The PCL-5[12] is a checklist of problems that people sometimes have in response to a very stressful experience. Subjects need to indicate a number to the right of each problem to indicate how much they have been bothered by that problem in the past month. The scale rates items from 0 (not at all), 1 (a little bit), 2 (moderately), 3 (quite a bit), and 4 (extremely). A sample of the PCL-5 is provided in Appendix 9.

3.7.2.5 Hospital Anxiety and Depression Scale (HADS)

The HADS[13] is a subject-rated scale designed to screen for anxiety and depressive states in medical subjects. The HADS consists of 2 subscales: The D-scale measures depression and the A-scale measures anxiety. Each subscale contains 7 items, and each item is rated from 0 (absent) to 3 (maximum severity). The score of each subscale ranges from 0 to 21, and the subscales are analyzed separately. It takes approximately 5 to 10 minutes to complete the HADS. A sample of the HADS is provided in Appendix 10.

3.7.2.6 Wearable Device

Use of the wearable device is optional and does not require a separate consent form. If the subject agrees to its use, the wearable device should be put on the subject's nondominant wrist at the Baseline (Day 0) Visit. The wearable device is to be worn continuously throughout the double-blind treatment period. At each trial visit, the wearable device is taken off, the data will be downloaded to the computer and the device will be placed back on the subject's nondominant wrist. At the Week 12/ET Visit, the wearable device monitoring will be stopped and the device returned to the trial site. All data from device should be transferred to Phillips by the conclusion of the Week 12/ET Visit.

3.7.2.7 Other Assessments

3.7.2.7.1 Emory Treatment Resistance Interview for PTSD (E-TRIP)

The E-TRIP[14] consists of clinician-administered questions to assess the adequacy and benefit derived from past treatment trials. For each adequately delivered treatment to which the subject failed to respond, a score is assigned depending on the strength of evidence supporting the treatment's efficacy. A copy of the score sheet is provided in Appendix 11.

3.7.2.7.2 Life Events Checklist for DSM-5 (LEC-5)

The LEC-5[15] is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. A copy of the score sheet is provided in Appendix 12.

3.7.2.7.3 Mini International Neuropsychiatric Interview (MINI)

The MINI[16,17,18,19] will be conducted at the Screening Visit to confirm the subject's diagnosis of PTSD and to rule out exclusionary comorbid psychiatric diagnoses. Detailed instructions for administration of this structured interview will be provided. A copy of the score sheet is provided in Appendix 13.

3.7.2.7.4 Ohio State University Traumatic Brain Injury Identification Method

The OSU TBI-ID[20] is a standardized procedure for eliciting a person's lifetime history of TBI via a 3-5 minute structured interview. A copy of the score sheet is provided in Safety Assessments Appendix 14.

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. If a fasting blood sample was not obtained at the Screening Visit and if more than 10 days have elapsed since the Screening Visit, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], HbA1c, TSH with reflex to T_4 if the result for TSH is abnormal, insulin, and urinalysis) need to be repeated at the Baseline (Day 0) Visit. The results of these tests at screening must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory will be retained electronically within the lab vendor's online portal and assessed by the investigator or qualified designee for clinical significance within eSource.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Hematocrit MCHC MCV RBC count WBC count with differential Platelet count Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity Ketones Urine Drug Screens: Amphetamines/MDMA Barbiturates Benzodiazepines Cannabinoids Cocaine Methadone Opiates Phencyclidine Propoxyphene Drug and alcohol Screening Blood alcohol	Serum Chemistry: ALP ALT AST Bilirubin, total BUN Calcium Cholesterol (total, LDL, and HDL) CPK Creatinine GGT Glucose LDH Potassium Prolactin[a] Protein, total Sodium Triglycerides Insulin Chloride Magnesium Bicarbonate Inorganic phosphorus Uric acid Albumin Additional Tests: Urine pregnancy for WOCBP TSH HbA1c Additional Tests (screening only): HIV HBsAg Anti-HCV

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HDL = high density lipoprotein; LDH = lactic dehydrogenase; LDL = low density lipoprotein; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; MDMA = methylenedioxymethamphetamine; WBC = white blood cell.

[a]Prolactin results will be blinded to the investigators and trial staff.

Any value outside the normal range will be flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory tests should be performed if clinically significant abnormalities are observed. Unscheduled laboratory

tests may be repeated at any time at the discretion of the investigator for appropriate medical care. Refer to Appendix 2 for criteria for identifying values of potential clinical relevance.

The following laboratory test results at screening are exclusionary:

- Platelets ≤ 75000/mm^3
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute ≤ 1000/mm^3
- Aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 2 × ULN
- Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
- Creatinine ≥ 2 mg/dL

The total volume of blood to be collected during the trial is expected to be approximately 100 - 115 mL.

A pregnancy test will be conducted in WOCBP prior to trial intervention; results must be available prior to the administration of the IMP. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

3.7.3.3 Physical Examination and Vital Signs

3.7.3.3.1 Physical Examination

A complete physical examination will consist of measurement of height and waist circumference and a review of the following body systems: head, eyes, ears, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae. Height will be measured with a stadiometer, measuring stick, or tape. Waist circumference will be measured with each physical examination. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- The waist circumference measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the

skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[21]

The principal investigator or his/her appointed designee is primarily responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be included on the FDA Form 1572. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

3.7.3.3.2 Measurement of Vital Signs

Measurement of vital signs will include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. The following guidelines will aid in the standardization of body weight measurements:

- The same scale should be used to weigh a given subject each time, if possible.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight should be recorded before a subject's meal and at approximately the same time at each visit.

Blood pressure and heart rate measurements will be made in the supine and standing positions after the subject has been in each position for at least 3 minutes. The supine measurements will be performed first followed by standing.

Subjects with uncontrolled hypertension (screening DBP > 95 mmHg in any position) or symptomatic hypotension are excluded from the trial as are subjects with orthostatic hypotension defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure **OR** development of symptoms (see Table 3.4.3-1). In addition, subjects should be excluded if they have any other vital sign measurement at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Appendix 3 is included to assist

investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

3.7.3.4 Electrocardiogram Assessments

All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review the ECG tracing and cardiology report within the central ECG vendor's online portal, assess the findings, noting whether or not any abnormal results are clinically significant within eSource.

The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis.

If, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject and/or the interpretation of the trial results) or meets an exclusion criterion (see Table 3.4.3-1), the subject should be excluded from the trial. Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Each ECG recording should be taken approximately 5 minutes apart (the ECG result reported will be evaluated at each time point). The central ECG service will provide the corrections for the 3 ECGs performed. Based on the QT interval as corrected by Fridericia's formula (QTcF) reported by the central service, a subject will be excluded if the corrections are $\geq$ 450 msec in men and $\geq$ 470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing. If only 1 ECG time point has a QTcF of $\geq$ 450 msec in men and $\geq$ 470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the trial.

Refer to Appendix 4 for a list of potentially clinically relevant ECG abnormalities to guide investigators for the assessment of potential ECG abnormalities for clinical significance postrandomization. Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. Please consult the medical monitor in case of questions.

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3.7.3.5 Other Safety Assessments

3.7.3.5.1 Abnormal Involuntary Movement Scale

The AIMS[22] assessment (Appendix 15) consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject's dental status. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Section 4.1). Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

3.7.3.5.2 Barnes Rating Scale For Drug-induced Akathisia

The BARS[23] (Appendix 16) consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Section 4.1). Investigators are encouraged to delay scale administration until

12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

The BARS Global Score is defined as the global clinical assessment of akathisia.

3.7.3.5.3 Simpson-Angus Scale

The SAS[24] (Appendix 17) consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5 point scale, with a score of zero representing absence of symptoms, and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Section 4.1). Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the SAS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

3.7.3.5.4 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "baseline/screening" and "Since Last Visit" versions of the scale. The "baseline/screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Table 3.4.3-1). The "Since Last Visit" C-SSRS form will also be completed at all visits after screening. Copies of the C-SSRS forms are provided in Appendix 18 and Appendix 19.

3.7.3.5.5 Deoxyribonucleic Acid (DNA) Blood Samples for Pharmacogenomic Testing

A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7-1) in order to extract deoxyribonucleic acid (DNA) and determine genotypes and related phenotypes for CYP2D6. The method used to determine these genotypes also generates genotype data for additional genes related to

absorption, distribution, metabolism, and excretion (ADME) of the compound. Phenotyping of these additional genes is not currently planned but may be considered in the future. All samples will be shipped to the central lab provided in Appendix 1.

3.7.4 Pharmacokinetic Assessments

A PK sample will be collected at Week 6 and Week 12 at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling.

3.7.4.1 Pharmacokinetic Blood Samples

All blood samples will be shipped to the testing facility for analysis. Detailed handling and shipping instructions are provided in Appendix 1.

3.7.5 Future Biospecimen Research

A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7-1) from consenting subjects, and if allowed by the IRB/IEC. Research performed on this sample may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

Processing, storage, and shipping instructions for FBR samples are provided in Appendix 1.

3.7.6 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up eSource for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

In this approximately 3 month trial, it is expected that subjects may have one or more treatment interruptions during the treatment phase. If a subject's IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery; dental work, or a temporary situation that prevents subject compliance with the IMP dosing schedule), the subject's IMP should be resumed as early as the situation allows (see Section 3.8.3.4). If > 4 consecutive doses of IMP are missed, a discussion should occur with the medical monitor to determine if the subject should be discontinued from the trial as a result of the treatment interruption.

3.8.3.2 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.5.

3.8.3.3 Documenting Reasons for Treatment Interruption/Discontinuation

A subject may temporarily interrupt or permanently discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
    - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard

  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
  - SAE
  - Other potentially IMP-related safety concerns or AEs
- Death
- Withdrawal of informed consent
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

If the subject temporarily interrupts or permanently discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 3.8.3.1 or Section 3.8.3.2 must be followed.

3.8.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, as possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up (these methods of follow-up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail,

or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).

- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1 and Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented (ie, subject who completes the consent process), but who is not randomized or assigned IMP.

Screen failures due to exclusionary criteria may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, additional 14-day extension(s) of screening may be requested from the medical monitor. Any extension should be requested prior to the expiration of the previous extension screening period, as applicable. If no extension

is granted, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. Subjects may be rescreened twice for this trial.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Week 12 Visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the Week 12 Visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also noncompliant and should be considered for discontinuation. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP.

Table 4.1-1 List of Medications Prohibited Before the Trial (Prior to Day 0)

1.	Neuroleptic agents (depot or long-acting injectable)	One full cycle plus 1/2 cycle
2.	Cariprazine, fluoxetine	28 days
3.	Monoamine oxidase inhibitor	14 days
4.	Antipsychotic agents (oral), antidepressants (expect fluoxetine, monoamine oxidase inhibitors and sertraline [if not at an adequate dose/duration)	7 days
5.	Benzodiazepines	7 days
6.	Hypnotics, including non-benzodiazepine sleep aids	7 days
7.	Mood stabilizers (ie, lithium and anticonvulsants)	7 days

Table 4.1-2 lists all medications prohibited during the trial, including exceptions, where appropriate.

Table 4.1-2 List of Medications Prohibited/Restricted During the Trial

1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Anticonvulsants c) Antidepressants d) Mood stabilizers (ie, lithium) e) Benzodiazepines, except when used to manage TEAEs such as agitation and anxiety[a] f) Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage TEAEs related to insomnia[b] g) Stimulants and atomoxetine – allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to Baseline (Day 0) Visit. Should be continued throughout trial participation. h) Opioid analgesics, unless approval is obtained from the medical monitor. Approval for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, etc) j) Disulfiram k) Prazosin - allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to Baseline (Day 0) Visit. Should be continued throughout trial participation
2.	Investigational agents within 60 days prior to Baseline (Day 0) Visit.
3.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers. Selected CYP2D6 inhibitors are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, clomipramine, pyrilamine, diphenhydramine, quinidine, terbinafine, halofantrine, tripelennamine. Selected CYP3A4 inhibitors are: amiodarone, fluvoxamine, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, nefazodone, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, verapamil. Selected CYP3A4 inducers are: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, troglitazone. The medical monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial.
4.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.

[a]Administration of specific oral benzodiazepines is permitted for the short-term management of TEAEs such as anxiety and agitation up to a maximum of 6 mg/day lorazepam (or equivalent) in divided doses. Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg alprazolam = 5 mg diazepam = 0.5 mg clonazepam. The prescribed benzodiazepine should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion to avoid any withdrawal effects. Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and

the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eSource.

[b]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of TEAEs related to insomnia for up to 4 days per week, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eSource.

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). The investigator should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator. In particular, the investigator should caution the subject about concomitant use of the following during the trial:

- Non-steroidal anti-inflammatory drugs, aspirin, or other drugs that interfere with coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of upper gastrointestinal bleeding.[25]
- Triptans (eg, sumatriptan, naratriptan, almotriptan, frovatriptan, rizatriptan, eletriptan, and zolmitriptan), linezolid, and methylene blue since there have been rare post-marketing reports of serotonin syndrome or serotonin syndrome-like reactions (eg, mental status changes, hyperreflexia, autonomic effects, lack of coordination, and diarrhea) following the concomitant use of SSRIs or serotonin-norepinephrine reuptake inhibitors and these drugs.[26,27,28]

Electroconvulsive therapy and transcranial magnetic stimulation are prohibited within 60 days of screening. In addition, subjects may not undergo implantation of a device for vagus nerve stimulation or deep brain stimulation during the trial.

Use of intramuscular benzodiazepines is prohibited throughout the trial. Continual use of oral benzodiazepines is also not permitted during the trial and subjects must discontinue benzodiazepines for at least 7 days prior to the Baseline (Day 0) Visit. However, administration of specific oral benzodiazepines is permitted for the short-term management of TEAEs such as anxiety and agitation up to a maximum of 6 mg/day lorazepam (or equivalent) in divided doses. Short-acting benzodiazepines are to be used whenever possible. If no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg alprazolam = 5 mg diazepam = 0.5 mg clonazepam. The prescribed benzodiazepine should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion to avoid any withdrawal effects.

Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of TEAEs related to insomnia for up to 4 days per week total during the treatment period, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication and the prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia.

Anticholinergics are permitted for the treatment of EPS up to a maximum of 4 mg/day benztropine or its equivalent and propranolol is permitted for akathisia or tremor up to a maximum of 20 mg 3 times daily (total of 60 mg/day). Sites should only utilize medications that are approved for these indications.

Benzodiazepines, non-benzodiazepine sleep aids, anticholinergics, and propranolol must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

All trial personnel should be familiar with the content of the IB for brexpiprazole in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

4.2.2 Non-therapy Precautions and Restrictions

4.2.2.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.

4.2.2.2 Restrictions

Subjects may only receive psychotherapy (including but not limited to: individual, group, marriage, family, EMDR therapy, pet therapy, etc.) if they have been participating in the therapy regularly for at least 28 days prior to screening and commit to maintain their participation during the course of the trial at the current frequency or unless permission is obtained from the medical monitor.

Consumption of grapefruit, grapefruit products, Seville oranges, or Seville orange products within 72 hours prior to dosing and during the trial is prohibited. Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial. The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death

- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential drug-induced liver injury (DILI) case (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional

tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eSource. The intensity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eSource provided by the sponsor. All AE collection is to begin after a subject completes the consent process.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

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5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, AE related to occupational exposure, DILI, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Drug-Induced Liver Injury

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eSource.

5.5 Pregnancy

Women of childbearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months with no menses without an alternative medical cause).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months with no menses without an alternative medical cause; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine and/or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all WOCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department (see the cover page of this protocol for contact information).

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/clinical research organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs and IREs up to 14 (+ 2) days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eSource page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eSource page according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has been resolved, stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact

Any new SAEs or IREs reported to the investigator which occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic/Pharmacogenomic Analysis

Pharmacokinetic samples will be analyzed for brexpiprazole (OPC-34712) and its metabolite(s) and descriptive statistics will be calculated. No formal statistical comparisons are planned. A separate population or pharmacokinetic/pharmacodynamic modeling may be performed using the data from this trial and other trials.

7 Statistical Analysis

Complete details of the planned statistical analysis will be presented in the unblinded addendum to this protocol and in the statistical analysis plan (SAP).

7.1 Sample Size

It is anticipated that approximately 332 subjects will be enrolled from an estimated 45 sites in the US.

7.1.1 Efficacy Analysis

The efficacy sample will be the full analysis set based on the intent-to-treat principle, which includes all randomly assigned subjects who take at least one dose of IMP (ie, the safety sample) and who have both a randomization and at least one post randomization non-missing value for CAPS-5 total score.

The change from baseline in CAPS-5 total score will be analyzed using a mixed-effect model repeated measures (MMRM) methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial center, type of trauma, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CAPS-5 total score by visit week as a covariate. The primary efficacy outcome measure is the mean change from baseline in the CAPS-5 total score.

Other continuous efficacy endpoints will also be analyzed using MMRM methodology. Complete model details will be specified in the SAP.

7.2 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (C-SSRS) and EPS (eg, the SAS, AIMS, and BARS). Safety analysis will be conducted based on the Safety Sample defined in Section 7.1.1. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.

7.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized by treatment group:

- TEAEs

- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.2.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements and prolactin concentrations will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined in the SAP criteria for laboratory tests will be summarized.

7.2.3 Physical Examination and Vital Signs Data

Physical examination findings will be listed by subject. Potentially clinically relevant results in vital signs and body weight will also be summarized.

Summary statistics for change from baseline in vital signs, body weight, and waist circumference will be provided.

7.2.4 Electrocardiogram Data

Mean change from baseline will be summarized by treatment group and by visit.

Incidence of clinically relevant changes will be calculated for ECG parameters and summarized by treatment group and by visit.

For the analysis of QT and QTc data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula:

$QTcB=QT/(RR)^{0.5}$, and

2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula:
$QTcF=QT/(RR)^{0.33}$

3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

Results will be summarized by visit.

7.2.5 Other Safety Data

Change from baseline in scores for EPS (eg, SAS, AIMS, and BARS) will be evaluated using analysis of covariance with baseline value as covariate and treatment as main factors. The analyses will be based on the observed case (OC) and last observation carried forward datasets of the Safety Sample.

Suicidality (eg, C-SSRS) will be summarized by treatment group based on the OC dataset of the Safety Sample. Details will be described in SAP.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPC- 34712 IB[5] and Zoloft prescribing information.[6]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP will be supplied as blister cards. Each blister card used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored according to the storage conditions indicated on the clinical label(s). The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

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8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially‑used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial site(s). The IMP may be destroyed by the trial site(s), only if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return or destruction (if applicable) of used IMP containers, unused IMP, and partially-used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online – Send information required for reporting purposes (listed below) to [redacted]
- Phone - Rocky Mountain Call Center at [redacted].

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (ID) (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

Source document and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application - rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly

entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be safety laboratory data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source record will take place, however on-site monitoring inspections will continue to take place in order to review data entry source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

The FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all

trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of data in the eSource application with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eSource, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting

subject privacy. To this end, a subject number and subject ID code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in the eSource application. If further subject ID is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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Appendix 1 Handling and Shipment of Bioanalytical Samples

Pharmacokinetic Sample Collection

Four mL of blood for PK testing will be collected into 4-mL Vacutainer tubes containing sodium heparin. Each tube should be gently inverted three to four times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from the tube should then be divided equally between the 2 bar-code labeled polypropylene tubes.

All tubes must be labeled using the central lab's bar-code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the PK sample information. It is important to note the exact date and time of the blood collection, the date and time of the last dose of brexpiprazole/placebo prior to each blood draw, and the time of the meal closest to the last dose.

The sample must be stored at −70°C, if available, or −20°C or below. If only a −20°C freezer is available, samples must be shipped within 30 days of collection. Primary and backup samples may be shipped together. If samples are stored in a −70°C freezer, then one tube (primary sample) will be shipped on dry ice to the central lab as soon as possible after collection. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab.

If neither a −70°C nor −20°C freezer is available, the primary and backup PK samples must be shipped on dry ice in the same box to the central laboratory on the day of collection.

Pharmacogenomic Sample Collection

A 10-mL whole blood sample for the pharmacogenomic determination of drug metabolizing enzymes and transporters and/or banking for future analysis will be collected by venipuncture into one 10-mL potassium ethylenediaminetetraacetic acid (K_2EDTA) Vacutainer tube. Each tube should be gently inverted 10 times to ensure proper mixing with the anticoagulant. Refrigerate the whole blood samples at 4°C for at least 1 day (but no longer than 4 days). Then, the samples should be stored upright at −20°C or below. If refrigerating is not possible, samples can be frozen directly from ambient. The tube will be shipped on dry ice to the central laboratory; the central laboratory will forward the sample to the pharmacogenomics laboratory.

Pharmacokinetic and Pharmacogenomic Sample Shipment

Plasma or whole blood samples must be neatly packed in the kits provided by the central lab and restrained in a Styrofoam container (place Styrofoam container supplied within a cardboard box). Boxes should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. The central laboratory must be alerted of sample shipment. Packages must not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC. Shipments from clinical sites will be via an overnight carrier to the central laboratory.

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x ULN
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
Lactate dehydrogenase	≥ 3 x ULN
Blood urea nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
Creatine phosphokinase	> 3 x ULN
Prolactin	> ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
WBC count	≤ 2,800 mm3 or ≥ 16,000 mm3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,500/mm^3
Platelet count	≤ 75,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Nonfasting	≥ 200 mg/dL
Total cholesterol, fasting	≥ 240 mg/dL
LDL cholesterol, fasting	≥ 160 mg/dL
HDL cholesterol, fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, fasting	≥150 mg/dL

ULN = upper limit of normal

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Appendix 3 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic blood pressure[b]	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic blood pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Orthostatic hypotension	≥ 20 mmHg decrease in systolic blood pressure and a ≥ 25 bpm increase in heart rate from supine to sitting/standing	Not applicable (baseline status not considered)
Weight	–	≥ 7% increase ≥ 7% decrease

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b]As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original New Drug Application Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

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Appendix 4 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post trial entry
ST/T Morphological		
Myocardial ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTcF ≥ 450 msec (men) QTcF ≥ 470 msec (women)	

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b]No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c]No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d]No current diagnosis of left bundle-branch block or right bundle-branch block.

Protocol 331-201-00061

Appendix 5 Past Month Version of the Clinician-Administered PTSD Scale For DSM-5 (CAPS-5)

National Center for PTSD

CLINICIAN-ADMINISTERED PTSD SCALE FOR DSM-5

PAST MONTH VERSION

Name: _____ ID#: _____

Interviewer: _____ Date: _____

Study: _____

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National Center for Posttraumatic Stress Disorder
May 1, 2015

Instructions

Standard administration and scoring of the CAPS-5 are essential for producing reliable and valid scores and diagnostic decisions. The CAPS-5 should be administered only by qualified interviewers who have formal training in structured clinical interviewing and differential diagnosis, a thorough understanding of the conceptual basis of PTSD and its various symptoms, and detailed knowledge of the features and conventions of the CAPS-5 itself.

Administration

1. Identify an index traumatic event to serve as the basis for symptom inquiry. Administer the Life Events Checklist and Criterion A inquiry provided on p. 5, or use some other structured, evidence-based method. The index event may involve either a single incident (e.g., "the accident") or multiple, closely related incidents (e.g., "the worst parts of your combat experiences").

2. Read prompts verbatim, one at a time, and in the order presented, EXCEPT:

   a. Use the respondent's own words for labeling the index event or describing specific symptoms.

   b. Rephrase standard prompts to acknowledge previously reported information, but return to verbatim phrasing as soon as possible. For example, inquiry for item 20 might begin: "You already mentioned having problems sleeping. What kinds of problems?"

   c. If you don't have sufficient information after exhausting all standard prompts, follow up ad lib. In this situation, repeating the initial prompt often helps refocus the respondent.

   d. As needed, ask for specific examples or direct the respondent to elaborate even when such prompts are not provided explicitly.

3. In general, DO NOT suggest responses. If a respondent has pronounced difficulty understanding a prompt it may be necessary to offer a brief example to clarify and illustrate. However, this should be done rarely and only after the respondent has been given ample opportunity to answer spontaneously.

4. DO NOT read rating scale anchors to the respondent. They are intended only for you, the interviewer, because appropriate use requires clinical judgment and a thorough understanding of CAPS-5 scoring conventions.

5. Move through the interview as efficiently as possible to minimize respondent burden. Some useful strategies:

   a. Be thoroughly familiar with the CAPS-5 so that prompts flow smoothly.

   b. Ask the fewest number of prompts needed to obtain sufficient information to support a valid rating.

   c. Minimize note-taking and write while the respondent is talking to avoid long pauses.

   d. Take charge of the interview. Be respectful but firm in keeping the respondent on task, transitioning between questions, pressing for examples, or pointing out contradictions.

Scoring

1. As with previous versions of the CAPS, CAPS-5 symptom severity ratings are based on symptom frequency and intensity, except for items 8 (amnesia) and 12 (diminished interest), which are based on amount and intensity. However, CAPS-5 items are rated with a single severity score, in contrast to previous versions of the CAPS which required separate frequency and intensity scores for each item that were either summed to create a symptom severity score or combined in various scoring rules to create a dichotomous (present/absent) symptom score. Thus, on the

CAPS-5 the clinician combines information about frequency and intensity before making a single severity rating. Depending on the item, frequency is rated as either the number of occurrences (how often in the past month) or percent of time (how much of the time in the past month). Intensity is rated on a four-point ordinal scale with ratings of *Minimal*, *Clearly Present*, *Pronounced*, and *Extreme*. Intensity and severity are related but distinct. Intensity refers to the strength of a typical occurrence of a symptom. Severity refers to the total symptom load over a given time period, and is a combination of intensity and frequency. This is similar to the quantity/frequency assessment approach to alcohol consumption. In general, intensity rating anchors correspond to severity scale anchors described below and should be interpreted and used in the same way, except that severity ratings require joint consideration of intensity and frequency. Thus, before taking frequency into account, an intensity rating of *Minimal* corresponds to a severity rating of *Mild / subthreshold*, *Clearly Present* corresponds with *Moderate / threshold*, *Pronounced* corresponds with *Severe / markedly elevated*, and *Extreme* corresponds with *Extreme / incapacitating*.

2. The five-point CAPS-5 symptom severity rating scale is used for all symptoms. Rating scale anchors should be interpreted and used as follows:

   0 ***Absent*** The respondent denied the problem or the respondent's report doesn't fit the DSM-5 symptom criterion.

   1 ***Mild / subthreshold*** The respondent described a problem that is consistent with the symptom criterion but isn't severe enough to be considered clinically significant. The problem doesn't satisfy the DSM-5 symptom criterion and thus doesn't count toward a PTSD diagnosis.

   2 ***Moderate / threshold*** The respondent described a clinically significant problem. The problem satisfies the DSM-5 symptom criterion and thus counts toward a PTSD diagnosis. The problem would be a target for intervention. This rating requires a minimum frequency of *2 X month* or *some of the time (20-30%)* PLUS a minimum intensity of *Clearly Present*.

   3 ***Severe / markedly elevated*** The respondent described a problem that is well above threshold. The problem is difficult to manage and at times overwhelming, and would be a prominent target for intervention. This rating requires a minimum frequency of *2 X week* or *much of the time (50-60%)* PLUS a minimum intensity of *Pronounced*.

   4 ***Extreme / incapacitating*** The respondent described a dramatic symptom, far above threshold. The problem is pervasive, unmanageable, and overwhelming, and would be a high-priority target for intervention.

3. In general, make a given severity rating only if the minimum frequency and intensity for that rating are both met. However, you may exercise clinical judgment in making a given severity rating if the reported frequency is somewhat lower than required, but the intensity is higher. For example, you may make a severity rating of *Moderate / threshold* if a symptom occurs *1 X month* (instead of the required *2 X month*) as long as intensity is rated *Pronounced* or *Extreme* (instead of the required *Clearly Present*). Similarly, you may make a severity rating of *Severe / markedly elevated* if a symptom occurs *1 X week* (instead of the required *2 X week*) as long as the intensity is rated *Extreme* (instead of the required *Pronounced*). If you are unable to decide between two severity ratings, make the lower rating.

4. You need to establish that a symptom not only meets the DSM-5 criterion phenomenologically, but is also functionally related to the index traumatic event, i.e., started or got worse as a result of the event. CAPS-5 items 1-8 and 10 (reexperiencing, effortful avoidance, amnesia, and blame) are inherently linked to the event. Evaluate the remaining items for trauma-relatedness (TR) using the TR inquiry and rating scale. The three TR ratings are:

   a. ***Definite*** = the symptom can clearly be attributed to the index trauma, because (1) there is an obvious change from the pre-trauma level of functioning and/or (2) the respondent makes the attribution to the index trauma with confidence.

   b. ***Probable*** = the symptom is likely related to the index trauma, but an unequivocal connection can't be made. Situations in which this rating would be given include the following: (1) there seems to be a change from the pre-

trauma level of functioning, but it isn't as clear and explicit as it would be for a "definite;" (2) the respondent attributes a causal link between the symptom and the index trauma, but with less confidence than for a rating of *Definite*; (3) there appears to be a functional relationship between the symptom and inherently trauma-linked symptoms such as reexperiencing symptoms (e.g., numbing or withdrawal increases when reexperiencing increases).

c. ***Unlikely*** = the symptom can be attributed to a cause other than the index trauma because (1) there is an obvious functional link with this other cause and/or (2) the respondent makes a confident attribution to this other cause and denies a link to the index trauma. Because it can be difficult to rule out a functional link between a symptom and the index trauma, a rating of *Unlikely* should be used only when the available evidence strongly points to a cause other than the index trauma. NOTE: Symptoms with a TR rating of *Unlikely* should not be counted toward a PTSD diagnosis or included in the total CAPS-5 symptom severity score.

5. **CAPS-5 total symptom severity score** is calculated by summing severity scores for items 1-20. NOTE: Severity scores for the two dissociation items (29 and 30) should NOT be included in the calculation of the total CAPS-5 severity score.

6. **CAPS-5 symptom cluster severity scores** are calculated by summing the individual item severity scores for symptoms contained in a given DSM-5 cluster. Thus, the Criterion B (reexperiencing) severity score is the sum of the individual severity scores for items 1-5; the Criterion C (avoidance) severity score is the sum of items 6 and 7; the Criterion D (negative alterations in cognitions and mood) severity score is the sum of items 8-14; and the Criterion E (hyperarousal) severity score is the sum of items 15-20. A symptom cluster score may also be calculated for dissociation by summing items 29 and 30.

7. **PTSD diagnostic status** is determined by first dichotomizing individual symptoms as "present" or "absent," then following the DSM-5 diagnostic rule. A symptom is considered present only if the corresponding item severity score is rated *2=Moderate/threshold* or higher. Items 9 and 11-20 have the additional requirement of a trauma-relatedness rating of *Definite* or *Probable*. Otherwise a symptom is considered absent. The DSM-5 diagnostic rule requires the presence of least one Criterion B symptom, one Criterion C symptom, two Criterion D symptoms, and two Criterion E symptoms. In addition, Criteria F and G must be met. Criterion F requires that the disturbance has lasted at least one month. Criterion G requires that the disturbance cause either clinically significant distress or functional impairment, as indicated by a rating of *2=moderate* or higher on items 23-25.

CAPS-5 Page 5

Criterion A: Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. **Directly experiencing the traumatic event(s).**
2. **Witnessing, in person, the event(s) as it occurred to others.**
3. **Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.**
4. **Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.**

[Administer Life Events Checklist or other structured trauma screen]

I'm going to ask you about the stressful experiences questionnaire you filled out. First I'll ask you to tell me a little bit about the event you said was the worst for you. Then I'll ask how that event may have affected you over the past month. In general I don't need a lot of information – just enough so I can understand any problems you may have had. Please let me know if you find yourself becoming upset as we go through the questions so we can slow down and talk about it. Also, let me know if you have any questions or don't understand something. Do you have any questions before we start?

The event you said was the worst was (EVENT). What I'd like for you to do is briefly describe what happened.

Index event (specify):

What happened? *(How old were you? How were you involved? Who else was involved? Was anyone seriously injured or killed? Was anyone's life in danger? How many times did this happen?)*	*Exposure type:* *Experienced ___* *Witnessed ___* *Learned about ___* *Exposed to aversive details___* *Life threat? NO YES [self ___ other ___]* *Serious injury? NO YES [self ___ other ___]* *Sexual violence? NO YES [self ___ other ___]* *Criterion A met? NO PROBABLE YES*

For the rest of the interview, I want you to keep (EVENT) in mind as I ask you about different problems it may have caused you. You may have had some of these problems before, but for this interview we're going to focus just on the past month. For each problem I'll ask if you've had it in the past month, and if so, how often and how much it bothered you.

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Criterion B: Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. (B1) Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

In the past month, have you had any unwanted memories of (EVENT) while you were awake, so not counting dreams? [Rate 0=Absent if only during dreams] **How does it happen that you start remembering (EVENT)?** [If not clear:] ***(Are these unwanted memories, or are you thinking about [EVENT] on purpose?)*** [Rate 0=Absent unless perceived as involuntary and intrusive] **How much do these memories bother you?** **Are you able to put them out of your mind and think about something else?** [If not clear:] ***(Overall, how much of a problem is this for you? How so?)*** Circle: Distress = *Minimal Clearly Present Pronounced Extreme* **How often have you had these memories in the past month?** *# of times*_____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 2 X month / distress clearly present, some difficulty dismissing memories Severe = at least 2 X week / pronounced distress, considerable difficulty dismissing memories	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

2. (B2) Recurrent distressing dreams in which the content and/or affect of the dream are related to the event(s). Note: In children, there may be frightening dreams without recognizable content.

In the past month, have you had any unpleasant dreams about (EVENT)? **Describe a typical dream.** *(What happens?)* [If not clear:] ***(Do they wake you up?)*** [If yes:] ***(What do you experience when you wake up? How long does it take you to get back to sleep?)*** [If reports not returning to sleep:] ***(How much sleep do you lose?)*** **How much do these dreams bother you?** Circle: Distress = *Minimal Clearly Present Pronounced Extreme* **How often have you had these dreams in the past month?** *# of times*_____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 2 X month / distress clearly present, less than 1 hour sleep loss Severe = at least 2 X week / pronounced distress, more than 1 hour sleep loss	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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3. (B3) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play.

In the past month, have there been times when you suddenly acted or felt as if (EVENT) were actually happening again? [If not clear:] ***(This is different than thinking about it or dreaming about it – now I'm asking about flashbacks, when you feel like you're actually back at the time of [EVENT], actually reliving it.)*** **How much does it seem as if (EVENT) were happening again?** *(Are you confused about where you actually are?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the past month?** *# of times* _____ ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 2 X month / dissociative quality clearly present, may retain some awareness of surroundings but relives event in a manner clearly distinct from thoughts and memories Severe = at least 2 X week / pronounced dissociative quality, reports vivid reliving, e.g., with images, sounds, smells	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

4. (B4) Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past month, have you gotten emotionally upset when something reminded you of (EVENT)? **What kinds of reminders make you upset?** **How much do these reminders bother you?** **Are you able to calm yourself down when this happens?** *(How long does it take?)* [If not clear:] ***(Overall, how much of a problem is this for you? How so?)*** Circle: Distress = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the past month?** *# of times* _____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 2 X month / distress clearly present, some difficulty recovering Severe = at least 2 X week / pronounced distress, considerable difficulty recovering	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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5. (B5) Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past month, have you had any physical reactions when something reminded you of (EVENT)? **Can you give me some examples?** *(Does your heart race or your breathing change? What about sweating or feeling really tense or shaky?)* **What kinds of reminders trigger these reactions?** **How long does it take you to recover?** Circle: Physiological reactivity = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often has this happened in the past month?** *# of times*_____ ***Key rating dimensions = frequency / intensity of physiological arousal*** Moderate = at least 2 X month / reactivity clearly present, some difficulty recovering Severe = at least 2 X week / pronounced reactivity, sustained arousal, considerable difficulty recovering	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

Criterion C: Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

6. (C1) Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the past month, have you tried to avoid thoughts or feelings about (EVENT)? **What kinds of thoughts or feelings do you avoid?** **How hard do you try to avoid these thoughts or feelings?** *(What kinds of things do you do?)* [if not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these thoughts or feelings?)*** Circle: Avoidance = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often in the past month?** *# of times*_____ ***Key rating dimensions = frequency / intensity of avoidance*** Moderate = at least 2 X month / avoidance clearly present Severe = at least 2 X week / pronounced avoidance	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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7. (C2) Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the past month, have you tried to avoid things that remind you of (EVENT), like certain people, places, or situations? **What kinds of things do you avoid?** **How much effort do you make to avoid these reminders?** *(Do you have to make a plan or change your activities to avoid them?)* [If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these reminders?)*** Circle: Avoidance = *Minimal Clearly Present Pronounced Extreme* **How often in the past month?** *# of times*_____ ***Key rating dimensions = frequency / intensity of avoidance*** Moderate = at least 2 X month / avoidance clearly present Severe = at least 2 X week / pronounced avoidance	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

Criterion D: Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

8. (D1) Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).

In the past month, have you had difficulty remembering some important parts of (EVENT)? *(Do you feel there are gaps in your memory of [EVENT]?)* **What parts have you had difficulty remembering?** **Do you feel you should be able to remember these things?** [If not clear:] ***(Why do you think you can't? Did you have a head injury during [EVENT]? Were you knocked unconscious? Were you intoxicated from alcohol or drugs?)*** [Rate 0=Absent if due to head injury or loss of consciousness or intoxication during event] [If still not clear:] ***(Is this just normal forgetting? Or do you think you may have blocked it out because it would be too painful to remember?)*** [Rate 0=Absent if due only to normal forgetting] Circle: Difficulty remembering = *Minimal Clearly Present Pronounced Extreme* **In the past month, how many of the important parts of (EVENT) have you had difficulty remembering?** *(What parts do you still remember?)* *# of important aspects* _____ **Would you be able to recall these things if you tried?** ***Key rating dimensions = amount of event not recalled / intensity of inability to recall*** Moderate = at least one important aspect / difficulty remembering clearly present, some recall possible with effort Severe = several important aspects / pronounced difficulty remembering, little recall even with effort	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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9. (D2) Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").

In the past month, have you had strong negative beliefs about yourself, other people, or the world? **Can you give me some examples?** *(What about believing things like "I am bad," "there is something seriously wrong with me," "no one can be trusted," "the world is completely dangerous"?)* **How strong are these beliefs?** *(How convinced are you that these beliefs are actually true? Can you see other ways of thinking about it?)* Circle: Conviction = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you felt that way, as a percentage?** *% of time*_____ **Did these beliefs start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of beliefs*** Moderate = some of the time (20-30%) / exaggerated negative expectations clearly present, some difficulty considering more realistic beliefs Severe = much of the time (50-60%) / pronounced exaggerated negative expectations, considerable difficulty considering more realistic beliefs	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

10. (D3) Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.

In the past month, have you blamed yourself for (EVENT) or what happened as a result of it? Tell me more about that. *(In what sense do you see yourself as having caused [EVENT]? Is it because of something you did? Or something you think you should have done but didn't? Is it because of something about you in general?)* **What about blaming someone else for (EVENT) or what happened as a result of it? Tell me more about that.** *(In what sense do you see [OTHERS] as having caused [EVENT]? Is it because of something they did? Or something you think they should have done but didn't?)* **How much do you blame (YOURSELF OR OTHERS)?** **How convinced are you that [YOU OR OTHERS] are truly to blame for what happened?** *(Do other people agree with you? Can you see other ways of thinking about it?)* [Rate 0=Absent if only blames perpetrator, i.e., someone who deliberately caused the event and intended harm] Circle: Conviction = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you felt that way, as a percentage?** *% of time*_____ ***Key rating dimensions = frequency / intensity of blame*** Moderate = some of the time (20-30%) / distorted blame clearly present, some difficulty considering more realistic beliefs Severe = much of the time (50-60%) / pronounced distorted blame, considerable difficulty considering more realistic beliefs	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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11. (D4) Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).

In the past month, have you had any strong negative feelings such as fear, horror, anger, guilt, or shame? **Can you give me some examples?** *(What negative feelings do you experience?)* **How strong are these negative feelings?** **How well are you able to manage them?** [If not clear:] ***(Overall, how much of a problem is this for you? How so?)*** Circle: Negative emotions = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you felt that way, as a percentage?** *% of time* _____ **Did these negative feelings start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of negative emotions*** Moderate = some of the time (20-30%) / negative emotions clearly present, some difficulty managing Severe = much of the time (50-60%) / pronounced negative emotions, considerable difficulty managing	0 *Absent* 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

12. (D5) Markedly diminished interest or participation in significant activities.

In the past month, have you been less interested in activities that you used to enjoy? **What kinds of things have you lost interest in or don't do as much as you used to?** *(Anything else?)* **Why is that?** [Rate 0=Absent if diminished participation is due to lack of opportunity, physical inability, or developmentally appropriate change in preferred activities] **How strong is your loss of interest?** *(Would you still enjoy [ACTIVITIES] once you got started?)* Circle: Loss of interest= *Minimal* *Clearly Present* *Pronounced* *Extreme* **Overall, in the past month, how many of your usual activities have you been less interested in, as a percentage?** *% of activities* _____ **What kinds of things do you still enjoy doing?** **Did this loss of interest start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = percent of activities affected / intensity of loss of interest*** Moderate = some activities (20-30%) / loss of interest clearly present but still has some enjoyment of activities Severe = many activities (50-60%) / pronounced loss of interest, little interest or participation in activities	0 *Absent* 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

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13. (D6) Feelings of detachment or estrangement from others

In the past month, have you felt distant or cut off from other people? **Tell me more about that.** **How strong are your feelings of being distant or cut off from others?** *(Who do you feel closest to? How many people do you feel comfortable talking with about personal things?)* Circle: Detachment or estrangement = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you felt that way, as a percentage?** *% of time* _____ **Did this feeling of being distant or cut off start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of detachment or estrangement*** Moderate = some of the time (20-30%) / feelings of detachment clearly present but still feels some interpersonal connection Severe = much of the time (50-60%) / pronounced feelings of detachment or estrangement from most people, may feel close to only one or two people	0 *Absent* 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

14. (D7) Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

In the past month, have there been times when you had difficulty experiencing positive feelings like love or happiness? **Tell me more about that.** *(What feelings are difficult to experience?)* **How much difficulty do you have experiencing positive feelings?** *(Are you still able to experience any positive feelings?)* Circle: Reduction of positive emotions = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you felt that way, as a percentage?** *% of time* _____ **Did this trouble experiencing positive feelings start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of reduction in positive emotions*** Moderate = some of the time (20-30%) / reduction of positive emotional experience clearly present but still able to experience some positive emotions Severe = much of the time (50-60%) / pronounced reduction of experience across range of positive emotions	0 *Absent* 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

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Criterion E: Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

15. (E1) Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.

In the past month, have there been times when you felt especially irritable or angry and showed it in your behavior? **Can you give me some examples?** *(How do you show it? Do you raise your voice or yell? Throw or hit things? Push or hit other people?)* Circle: Aggression = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often in the past month?** *# of times*_____ **Did this behavior start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of aggressive behavior*** Moderate = at least 2 X month / aggression clearly present, primarily verbal Severe = at least 2 X week / pronounced aggression, at least some physical aggression	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

16. (E2) Reckless or self-destructive behavior.

In the past month, have there been times when you were taking more risks or doing things that might have caused you harm? **Can you give me some examples?** **How much of a risk do you take?** *(How dangerous are these behaviors? Were you injured or harmed in some way?)* Circle: Risk = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often have you taken these kinds of risks in the past month?** *# of times*_____ **Did this behavior start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / degree of risk*** Moderate = at least 2 X month / risk clearly present, may have been harmed Severe = at least 2 X week / pronounced risk, actual harm or high probability of harm	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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17. (E3) Hypervigilance.

In the past month, have you been especially alert or watchful, even when there was no specific threat or danger? *(Have you felt as if you had to be on guard?)* **Can you give me some examples?** *(What kinds of things do you do when you're alert or watchful?)* [If not clear:] ***(What causes you to react this way? Do you feel like you're in danger or threatened in some way? Do you feel that way more than most people would in the same situation?)*** Circle: Hypervigilance = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you felt that way, as a percentage?** *% of time*_____ **Did being especially alert or watchful start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of hypervigilance*** Moderate = some of the time (20-30%) / hypervigilance clearly present, e.g., watchful in public, heightened awareness of threat Severe = much of the time (50-60%) / pronounced hypervigilance, e.g., scans environment for danger, may have safety rituals, exaggerated concern for safety of self/family/home	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

18. (E4) Exaggerated startle response.

In the past month, have you had any strong startle reactions? **What kinds of things made you startle?** **How strong are these startle reactions?** *(How strong are they compared to how most people would respond? Do you do anything other people would notice?)* **How long does it take you to recover?** Circle: Startle = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often has this happened in the past month?** *# of times*_____ **Did these startle reactions start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of startle*** Moderate = at least 2 X month / startle clearly present, some difficulty recovering Severe = at least 2 X week / pronounced startle, sustained arousal, considerable difficulty recovering	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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19. (E5) Problems with concentration.

In the past month, have you had any problems with concentration? **Can you give me some examples?** **Are you able to concentrate if you really try?** [If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have problems with concentration?)*** Circle: Problem concentrating = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past month have you had problems with concentration, as a percentage?** *% of time*_____ **Did these problems with concentration start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of concentration problems*** Moderate = some of the time (20-30%) / problem concentrating clearly present, some difficulty but can concentrate with effort Severe = much of the time (50-60%) / pronounced problem concentrating, considerable difficulty even with effort	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

20. (E6) Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

In the past month, have you had any problems falling or staying asleep? **What kinds of problems?** *(How long does it take you to fall asleep? How often do you wake up in the night? Do you wake up earlier than you want to?)* **How many total hours do you sleep each night?** **How many hours do you think you should be sleeping?** Circle: Problem sleeping = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often in the past month have you had these sleep problems?** *# of times*_____ **Did these sleep problems start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of sleep problems*** Moderate = at least 2 X month / sleep disturbance clearly present, clearly longer latency or clear difficulty staying asleep, 30-90 minutes loss of sleep Severe = at least 2 X week / pronounced sleep disturbance, considerably longer latency or marked difficulty staying asleep, 90 min to 3 hrs loss of sleep	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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Criterion F: Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

21. Onset of symptoms

(If not clear:) **When did you first start having (PTSD SYMPTOMS) you've told me about?** *(How long after the trauma did they start? More than six months?)*	*Total # months delay in onset* _____ *With delayed onset (> 6 months)? NO YES*

22. Duration of symptoms

(If not clear:) **How long have these (PTSD SYMPTOMS) lasted altogether?**	*Total # months duration* _____ *Duration more than 1 month? NO YES*

Criterion G: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

23. Subjective distress

Overall, in the past month, how much have you been bothered by these (PTSD SYMPTOMS) you've told me about? (Consider distress reported on earlier items)	0	*None*
	1	*Mild, minimal distress*
	2	*Moderate, distress clearly present but still manageable*
	3	*Severe, considerable distress*
	4	*Extreme, incapacitating distress*

24. Impairment in social functioning

In the past month, have these (PTSD SYMPTOMS) affected your relationships with other people? How so? (Consider impairment in social functioning reported on earlier items)	0	*No adverse impact*
	1	*Mild impact, minimal impairment in social functioning*
	2	*Moderate impact, definite impairment but many aspects of social functioning still intact*
	3	*Severe impact, marked impairment, few aspects of social functioning still intact*
	4	*Extreme impact, little or no social functioning*

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25. Impairment in occupational or other important area of functioning

[If not clear:] **Are you working now?** [If yes:] **In the past month, have these (PTSD SYMPTOMS) affected your work or your ability to work? How so?** [If no:] **Why is that?** *(Do you feel that your [PTSD SYMPTOMS] are related to you not working now? How so?)* [If unable to work because of PTSD symptoms, rate at least 3=Severe. If unemployment is not due to PTSD symptoms, or if the link is not clear, base rating only on impairment in other important areas of functioning] **Have these (PTSD SYMPTOMS) affected any other important part of your life?** (As appropriate, suggest examples such as parenting, housework, schoolwork, volunteer work, etc.) **How so?**	0 *No adverse impact* 1 *Mild impact, minimal impairment in occupational/other important functioning* 2 *Moderate impact, definite impairment but many aspects of occupational/other important functioning still intact* 3 *Severe impact, marked impairment, few aspects of occupational/other important functioning still intact* 4 *Extreme impact, little or no occupational/other important functioning*

Global Ratings

26. Global validity

Estimate the overall validity of responses. Consider factors such as compliance with the interview, mental status (e.g., problems with concentration, comprehension of items, dissociation), and evidence of efforts to exaggerate or minimize symptoms	0 *Excellent, no reason to suspect invalid responses* 1 *Good, factors present that may adversely affect validity* 2 *Fair, factors present that definitely reduce validity* 3 *Poor, substantially reduced validity* 4 *Invalid responses, severely impaired mental status or possible deliberate "faking bad" or "faking good"*

27. Global severity

Estimate the overall severity of PTSD symptoms. Consider degree of subjective distress, degree of functional impairment, observations of behaviors in interview, and judgment regarding reporting style.	0 *No clinically significant symptoms, no distress and no functional impairment* 1 *Mild, minimal distress or functional impairment* 2 *Moderate, definite distress or functional impairment but functions satisfactorily with effort* 3 *Severe, considerable distress or functional impairment, limited functioning even with effort* 4 *Extreme, marked distress or marked impairment in two or more major areas of functioning*

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28. Global improvement

Rate total overall improvement since the previous rating. Rate the degree of change, whether or not, in your judgment, it is due to treatment.	0 *Asymptomatic* 1 *Considerable improvement* 2 *Moderate improvement* 3 *Slight improvement* 4 *No improvement* 5 *Insufficient information*

Specify whether with dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

29. (1) Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

In the past month, have there been times when you felt as if you were separated from yourself, like you were watching yourself from the outside or observing your thoughts and feelings as if you were another person? [If no:] ***(What about feeling as if you were in a dream, even though you were awake? Feeling as if something about you wasn't real? Feeling as if time was moving more slowly?)*** **Tell me more about that.** **How strong is this feeling?** *(Do you lose track of where you actually are or what's actually going on?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme* [If not clear:] ***(Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?)*** [Rate 0=Absent if due to the effects of a substance or another medical condition] **How often has this happened in the past month?** *# of times*_____ **Did this feeling start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 2 X month / dissociative quality clearly present but transient, retains some realistic sense of self and awareness of environment Severe = at least 2 X week / pronounced dissociative quality, marked sense of detachment and unreality	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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30. (2) Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

In the past month, have there been times when things going on around you seemed unreal or very strange and unfamiliar? [If no:] ***(Do things going on around you seem like a dream or like a scene from a movie? Do they seem distant or distorted?)*** **Tell me more about that.** **How strong is this feeling?** *(Do you lose track of where you actually are or what's actually going on?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme* [If not clear:] ***(Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?)*** [Rate 0=Absent if due to the effects of a substance or another medical condition] **How often has this happened in the past month?** *# of times* _____ **Did this feeling start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 2 X month / dissociative quality clearly present but transient, retains some realistic sense of environment Severe = at least 2 X week / pronounced dissociative quality, marked sense of unreality	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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CAPS-5 SUMMARY SHEET

Name:_____ ID#:_____ Interviewer:_____ Study:_____ Date:_____

A. Exposure to actual or threatened death, serious injury, or sexual violence	
Criterion A met?	0 = NO 1 = YES

B. Intrusion symptoms (need 1 for diagnosis)	*Past Month*	
	Sev	*Sx (Sev ≥ 2)?*
(1) B1 – Intrusive memories		0 = NO 1 = YES
(2) B2 – Distressing dreams		0 = NO 1 = YES
(3) B3 – Dissociative reactions		0 = NO 1 = YES
(4) B4 – Cued psychological distress		0 = NO 1 = YES
(5) B5 – Cued physiological reactions		0 = NO 1 = YES
B subtotals	*B Sev =*	*# B Sx =*

C. Avoidance symptoms (need 1 for diagnosis)	*Past Month*	
	Sev	*Sx (Sev ≥ 2)?*
(6) C1 – Avoidance of memories, thoughts, feelings		0 = NO 1 = YES
(7) C2 – Avoidance of external reminders		0 = NO 1 = YES
C subtotals	*C Sev =*	*# C Sx =*

D. Cognitions and mood symptoms (need 2 for diagnosis)	*Past Month*	
	Sev	*Sx (Sev ≥ 2)?*
(8) D1 – Inability to recall important aspect of event		0 = NO 1 = YES
(9) D2 – Exaggerated negative beliefs or expectations		0 = NO 1 = YES
(10) D3 – Distorted cognitions leading to blame		0 = NO 1 = YES
(11) D4 – Persistent negative emotional state		0 = NO 1 = YES
(12) D5 – Diminished interest or participation in activities		0 = NO 1 = YES
(13) D6 – Detachment or estrangement from others		0 = NO 1 = YES
(14) D7 – Persistent inability to experience positive emotions		0 = NO 1 = YES
D subtotals	*D Sev =*	*# D Sx =*

E. Arousal and reactivity symptoms (need 2 for diagnosis)	*Past Month*	
	Sev	*Sx (Sev ≥ 2)?*
(15) E1 – Irritable behavior and angry outbursts		0 = NO 1 = YES
(16) E2 – Reckless or self-destructive behavior		0 = NO 1 = YES
(17) E3 – Hypervigilance		0 = NO 1 = YES
(18) E4 – Exaggerated startle response		0 = NO 1 = YES
(19) E5 – Problems with concentration		0 = NO 1 = YES
(20) E6 – Sleep disturbance		0 = NO 1 = YES
E subtotals	*E Sev =*	*# E Sx =*

PTSD totals	*Past Month*	
	Total Sev	*Total # Sx*
Sum of subtotals (B+C+D+E)		

F. Duration of disturbance	*Current*
(22) Duration of disturbance ≥ 1 month?	0 = NO 1 = YES

G. Distress or impairment (need 1 for diagnosis)	*Past Month*	
	Sev	*Cx (Sev ≥ 2)?*
(23) Subjective distress		0 = NO 1 = YES
(24) Impairment in social functioning		0 = NO 1 = YES
(25) Impairment in occupational functioning		0 = NO 1 = YES
G subtotals	*G Sev =*	*# G Cx =*

Global ratings	*Past Month*
(26) Global validity	
(27) Global severity	
(28) Global improvement	

Dissociative symptoms (need 1 for subtype)	*Past Month*	
	Sev	*Sx (Sev ≥ 2)?*
(29) 1 – Depersonalization		0 = NO 1 = YES
(30) 2 – Derealization		0 = NO 1 = YES
Dissociative subtotals	*Diss Sev =*	*# Diss Sx =*

PTSD diagnosis	*Past Month*
PTSD PRESENT – ALL CRITERIA (A-G) MET?	0 = NO 1 = YES
With dissociative symptoms	0 = NO 1 = YES
(21) With delayed onset (≥ 6 months)	0 = NO 1 = YES

Protocol 331-201-00061

Appendix 6 Past Week Version of the Clinician-Administered PTSD Scale For DSM-5 (CAPS-5)

National Center for PTSD

CLINICIAN-ADMINISTERED PTSD SCALE FOR DSM-5

PAST WEEK VERSION

Name: _____ ID#: _____

Interviewer: _____ Date: _____

Study: _____

Frank W. Weathers, Dudley D. Blake, Paula P. Schnurr,
Danny G. Kaloupek, Brian P. Marx, & Terence M. Keane

National Center for Posttraumatic Stress Disorder
May 1, 2015

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NOTE: This is the PAST WEEK version of the CAPS-5, which should be used only to evaluate PTSD symptom severity over the past week. PTSD diagnostic status should be evaluated with the PAST MONTH version of the CAPS-5.

Criterion A: Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. **Directly experiencing the traumatic event(s).**
2. **Witnessing, in person, the event(s) as it occurred to others.**
3. **Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.**
4. **Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.**

NOTE: Criterion A should already have been evaluated in a prior administration of the PAST MONTH version of the CAPS-5. Thus, for most applications of the PAST WEEK version, Criterion A does not need to be re-evaluated.

[Administer Life Events Checklist or other structured trauma screen]

I'm going to ask you about the stressful experiences questionnaire you filled out. First I'll ask you to tell me a little bit about the event you said was the worst for you. Then I'll ask how that event may have affected you over the past week. In general I don't need a lot of information – just enough so I can understand any problems you may have had. Please let me know if you find yourself becoming upset as we go through the questions so we can slow down and talk about it. Also, let me know if you have any questions or don't understand something. Do you have any questions before we start?

The event you said was the worst was (EVENT). What I'd like for you to do is briefly describe what happened.

Index event (specify):

What happened? *(How old were you? How were you involved? Who else was involved? Was anyone seriously injured or killed? Was anyone's life in danger? How many times did this happen?)*	*Exposure type:* *Experienced ___* *Witnessed ___* *Learned about ___* *Exposed to aversive details ___* *Life threat? NO YES [self ___ other ___]* *Serious injury? NO YES [self ___ other ___]* *Sexual violence? NO YES [self ___ other ___]* *Criterion A met? NO PROBABLE YES*

For the rest of the interview, I want you to keep (EVENT) in mind as I ask you about different problems it may have caused you. You may have had some of these problems before, but for this interview we're going to focus just on the past week. For each problem I'll ask if you've had it in the past <u>week,</u> and if so, how often and how much it bothered you.

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Criterion B: Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. (B1) Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

In the past week, have you had any unwanted memories of (EVENT) while you were awake, so not counting dreams? [Rate 0=Absent if only during dreams] **How does it happen that you start remembering (EVENT)?** [If not clear:] ***(Are these unwanted memories, or are you thinking about [EVENT] on purpose?)*** [Rate 0=Absent unless perceived as involuntary and intrusive] **How much do these memories bother you?** **Are you able to put them out of your mind and think about something else?** [If not clear:] ***(Overall, how much of a problem is this for you? How so?)*** Circle: Distress = *Minimal Clearly Present Pronounced Extreme* **How often have you had these memories in the past week?** *# of times* _____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 1 X week / distress clearly present, some difficulty dismissing memories Severe = at least 2 X week / pronounced distress, considerable difficulty dismissing memories	0 ***Absent*** 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

2. (B2) Recurrent distressing dreams in which the content and/or affect of the dream are related to the event(s). Note: In children, there may be frightening dreams without recognizable content.

In the past week, have you had any unpleasant dreams about (EVENT)? **Describe a typical dream.** *(What happens?)* [If not clear:] ***(Do they wake you up?)*** [If yes:] ***(What do you experience when you wake up? How long does it take you to get back to sleep?)*** [If reports not returning to sleep:] ***(How much sleep do you lose?)*** **How much do these dreams bother you?** Circle: Distress = *Minimal Clearly Present Pronounced Extreme* **How often have you had these dreams in the past week?** *# of times* _____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 1 X week / distress clearly present, less than 1 hour sleep loss Severe = at least 2 X week / pronounced distress, more than 1 hour sleep loss	0 ***Absent*** 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

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3. (B3) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play.

In the past week, have there been times when you suddenly acted or felt as if (EVENT) were actually happening again? [If not clear:] ***(This is different than thinking about it or dreaming about it – now I'm asking about flashbacks, when you feel like you're actually back at the time of [EVENT], actually reliving it.)*** **How much does it seem as if (EVENT) were happening again?** *(Are you confused about where you actually are?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the past week?** *# of times*_____ ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 1 X week / dissociative quality clearly present, may retain some awareness of surroundings but relives event in a manner clearly distinct from thoughts and memories Severe = at least 2 X week / pronounced dissociative quality, reports vivid reliving, e.g., with images, sounds, smells	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

4. (B4) Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past week, have you gotten emotionally upset when something reminded you of (EVENT)? **What kinds of reminders make you upset?** **How much do these reminders bother you?** **Are you able to calm yourself down when this happens?** *(How long does it take?)* [If not clear:] ***(Overall, how much of a problem is this for you? How so?)*** Circle: Distress = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the past week?** *# of times*_____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 1 X week / distress clearly present, some difficulty recovering Severe = at least 2 X week / pronounced distress, considerable difficulty recovering	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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5. (B5) Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past week, have you had any physical reactions when something reminded you of (EVENT)? **Can you give me some examples?** *(Does your heart race or your breathing change? What about sweating or feeling really tense or shaky?)* **What kinds of reminders trigger these reactions?** **How long does it take you to recover?** Circle: Physiological reactivity = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the past week?** *# of times*_____ ***Key rating dimensions = frequency / intensity of physiological arousal*** Moderate = at least 1 X week / reactivity clearly present, some difficulty recovering Severe = at least 2 X week / pronounced reactivity, sustained arousal, considerable difficulty recovering	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

Criterion C: Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

6. (C1) Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the past week, have you tried to avoid thoughts or feelings about (EVENT)? **What kinds of thoughts or feelings do you avoid?** **How hard do you try to avoid these thoughts or feelings?** *(What kinds of things do you do?)* [If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these thoughts or feelings?)*** Circle: Avoidance = *Minimal Clearly Present Pronounced Extreme* **How often in the past week?** *# of times*_____ ***Key rating dimensions = frequency / intensity of avoidance*** Moderate = at least 1 X week / avoidance clearly present Severe = at least 2 X week / pronounced avoidance	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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7. (C2) Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the past week, have you tried to avoid things that remind you of (EVENT), like certain people, places, or situations? **What kinds of things do you avoid?** **How much effort do you make to avoid these reminders?** *(Do you have to make a plan or change your activities to avoid them?)* [If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these reminders?)*** Circle: Avoidance = *Minimal Clearly Present Pronounced Extreme* **How often in the past week?** *# of times* _____ ***Key rating dimensions = frequency / intensity of avoidance*** Moderate = at least 1 X week / avoidance clearly present Severe = at least 2 X week / pronounced avoidance	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

Criterion D: Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

8. (D1) Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).

In the past week, have you had difficulty remembering some important parts of (EVENT)? *(Do you feel there are gaps in your memory of [EVENT]?)* **What parts have you had difficulty remembering?** **Do you feel you should be able to remember these things?** [If not clear:] ***(Why do you think you can't? Did you have a head injury during [EVENT]? Were you knocked unconscious? Were you intoxicated from alcohol or drugs?)*** [Rate 0=Absent if due to head injury or loss of consciousness or intoxication during event] [If still not clear:] ***(Is this just normal forgetting? Or do you think you may have blocked it out because it would be too painful to remember?)*** [Rate 0=Absent if due only to normal forgetting] Circle: Difficulty remembering = *Minimal Clearly Present Pronounced Extreme* **In the past week, how many of the important parts of (EVENT) have you had difficulty remembering?** *(What parts do you still remember?)* *# of important aspects* _____ **Would you be able to recall these things if you tried?** ***Key rating dimensions = amount of event not recalled / intensity of inability to recall*** Moderate = at least one important aspect / difficulty remembering clearly present, some recall possible with effort Severe = several important aspects / pronounced difficulty remembering, little recall even with effort	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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9. (D2) Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").

In the past week, have you had strong negative beliefs about yourself, other people, or the world? **Can you give me some examples?** *(What about believing things like "I am bad," "there is something seriously wrong with me," "no one can be trusted," "the world is completely dangerous"?)* **How strong are these beliefs?** *(How convinced are you that these beliefs are actually true? Can you see other ways of thinking about it?)* Circle: Conviction = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the past week have you felt that way, as a percentage?** *% of time* _____ **Did these beliefs start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of beliefs*** Moderate = some of the time (20-30%) / exaggerated negative expectations clearly present, some difficulty considering more realistic beliefs Severe = much of the time (50-60%) / pronounced exaggerated negative expectations, considerable difficulty considering more realistic beliefs	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

10. (D3) Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.

In the past week, have you blamed yourself for (EVENT) or what happened as a result of it? Tell me more about that. *(In what sense do you see yourself as having caused [EVENT]? Is it because of something you did? Or something you think you should have done but didn't? Is it because of something about you in general?)* **What about blaming someone else for (EVENT) or what happened as a result of it? Tell me more about that.** *(In what sense do you see [OTHERS] as having caused [EVENT]? Is it because of something they did? Or something you think they should have done but didn't?)* **How much do you blame (YOURSELF OR OTHERS)?** **How convinced are you that [YOU OR OTHERS] are truly to blame for what happened?** *(Do other people agree with you? Can you see other ways of thinking about it?)* [Rate 0=Absent if only blames perpetrator, i.e., someone who deliberately caused the event and intended harm] Circle: Conviction = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the past week have you felt that way, as a percentage?** *% of time* _____ ***Key rating dimensions = frequency / intensity of blame*** Moderate = some of the time (20-30%) / distorted blame clearly present, some difficulty considering more realistic beliefs Severe = much of the time (50-60%) / pronounced distorted blame, considerable difficulty considering more realistic beliefs	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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11. (D4) Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).

In the past week, have you had any strong negative feelings such as fear, horror, anger, guilt, or shame? **Can you give me some examples?** *(What negative feelings do you experience?)* **How strong are these negative feelings?** **How well are you able to manage them?** [If not clear:] ***(Overall, how much of a problem is this for you? How so?)*** Circle: Negative emotions = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past week have you felt that way, as a percentage?** *% of time* _____ **Did these negative feelings start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of negative emotions*** Moderate = some of the time (20-30%) / negative emotions clearly present, some difficulty managing Severe = much of the time (50-60%) / pronounced negative emotions, considerable difficulty managing	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

12. (D5) Markedly diminished interest or participation in significant activities.

In the past week, have you been less interested in activities that you used to enjoy? **What kinds of things have you lost interest in or don't do as much as you used to?** *(Anything else?)* **Why is that?** [Rate 0=Absent if diminished participation is due to lack of opportunity, physical inability, or developmentally appropriate change in preferred activities] **How strong is your loss of interest?** *(Would you still enjoy [ACTIVITIES] once you got started?)* Circle: Loss of interest= *Minimal* *Clearly Present* *Pronounced* *Extreme* **Overall, in the past week, how many of your usual activities have you been less interested in, as a percentage?** *% of activities* _____ **What kinds of things do you still enjoy doing?** **Did this loss of interest start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = percent of activities affected / intensity of loss of interest*** Moderate = some activities (20-30%) / loss of interest clearly present but still has some enjoyment of activities Severe = many activities (50-60%) / pronounced loss of interest, little interest or participation in activities	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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13. (D6) Feelings of detachment or estrangement from others.

In the past week, have you felt distant or cut off from other people? **Tell me more about that.** **How strong are your feelings of being distant or cut off from others?** *(Who do you feel closest to? How many people do you feel comfortable talking with about personal things?)* Circle: Detachment or estrangement = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past week have you felt that way, as a percentage?** *% of time* _____ **Did this feeling of being distant or cut off start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of detachment or estrangement*** Moderate = some of the time (20-30%) / feelings of detachment clearly present but still feels some interpersonal connection Severe = much of the time (50-60%) / pronounced feelings of detachment or estrangement from most people, may feel close to only one or two people	0 *Absent* 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

14. (D7) Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

In the past week, have there been times when you had difficulty experiencing positive feelings like love or happiness? **Tell me more about that.** *(What feelings are difficult to experience?)* **How much difficulty do you have experiencing positive feelings?** *(Are you still able to experience any positive feelings?)* Circle: Reduction of positive emotions = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past week have you felt that way, as a percentage?** *% of time* _____ **Did this trouble experiencing positive feelings start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of reduction in positive emotions*** Moderate = some of the time (20-30%) / reduction of positive emotional experience clearly present but still able to experience some positive emotions Severe = much of the time (50-60%) / pronounced reduction of experience across range of positive emotions	0 *Absent* 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

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Criterion E: Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

15. (E1) Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.

In the past week, have there been times when you felt especially irritable or angry and showed it in your behavior? **Can you give me some examples?** *(How do you show it? Do you raise your voice or yell? Throw or hit things? Push or hit other people?)* Circle: Aggression = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often in the past week?** *# of times* _____ **Did this behavior start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of aggressive behavior*** Moderate = at least 1 X week / aggression clearly present, primarily verbal Severe = at least 2 X week / pronounced aggression, at least some physical aggression	0 ***Absent*** 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

16. (E2) Reckless or self-destructive behavior

In the past week, have there been times when you were taking more risks or doing things that might have caused you harm? **Can you give me some examples?** **How much of a risk do you take?** *(How dangerous are these behaviors? Were you injured or harmed in some way?)* Circle: Risk = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often have you taken these kinds of risks in the past week?** *# of times* _____ **Did this behavior start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / degree of risk*** Moderate = at least 1 X week / risk clearly present, may have been harmed Severe = at least 2 X week / pronounced risk; actual harm or high probability of harm	0 ***Absent*** 1 ***Mild / subthreshold*** 2 ***Moderate / threshold*** 3 ***Severe / markedly elevated*** 4 ***Extreme / incapacitating***

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17. (E3) Hypervigilance.

In the past week, have you been especially alert or watchful, even when there was no specific threat or danger? *(Have you felt as if you had to be on guard?)* **Can you give me some examples?** *(What kinds of things do you do when you're alert or watchful?)* [If not clear:] ***(What causes you to react this way? Do you feel like you're in danger or threatened in some way? Do you feel that way more than most people would in the same situation?)*** Circle: Hypervigilance = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past week have you felt that way, as a percentage?** *% of time* _____ **Did being especially alert or watchful start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of hypervigilance*** Moderate = some of the time (20-30%) / hypervigilance clearly present, e.g., watchful in public; heightened awareness of threat Severe = much of the time (50-60%) / pronounced hypervigilance, e.g. scans environment for danger, may have safety rituals, exaggerated concern for safety of self/family/home	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

18. (E4) Exaggerated startle response.

In the past week, have you had any strong startle reactions? **What kinds of things made you startle?** **How strong are these startle reactions?** *(How strong are they compared to how most people would respond? Do you do anything other people would notice?)* **How long does it take you to recover?** Circle: Startle = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often has this happened in the past week?** *# of times* _____ **Did these startle reactions start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of startle*** Moderate = at least 1 X week / startle clearly present, some difficulty recovering Severe = at least 2 X week / pronounced startle, sustained arousal, considerable difficulty recovering	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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19. (E5) Problems with concentration

In the past week, have you had any problems with concentration? **Can you give me some examples?** **Are you able to concentrate if you really try?** [If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have problems with concentration?)*** Circle: Problem concentrating = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How much of the time in the past week have you had problems with concentration, as a percentage?** *% of time* _____ **Did these problems with concentration start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of concentration problems*** Moderate = some of the time (20-30%) / problem concentrating clearly present, some difficulty but can concentrate with effort Severe = much of the time (50-60%) / pronounced problem concentrating, considerable difficulty even with effort	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

20. (E6) Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

In the past week, have you had any problems falling or staying asleep? **What kinds of problems?** *(How long does it take you to fall asleep? How often do you wake up in the night? Do you wake up earlier than you want to?)* **How many total hours do you sleep each night?** **How many hours do you think you should be sleeping?** Circle: Problem sleeping = *Minimal* *Clearly Present* *Pronounced* *Extreme* **How often in the past week have you had these sleep problems?** *# of times* _____ **Did these sleep problems start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite* *Probable* *Unlikely* ***Key rating dimensions = frequency / intensity of sleep problems*** Moderate = at least 1 X week / sleep disturbance clearly present, clearly longer latency or clear difficulty staying asleep, 30-90 minutes loss of sleep Severe = at least 2 X week / pronounced sleep disturbance, considerably longer latency or marked difficulty staying asleep, 90 min to 3 hrs loss of sleep	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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Criterion F: Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

NOTE: Items 21 and 22 are not applicable for the PAST WEEK version. They are listed here without prompts only to maintain correspondence with item numbering on the PAST MONTH version. Onset and duration of symptoms should be assessed with

21. Onset of symptoms

22. Duration of symptoms

Criterion G: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

23. Subjective distress

Overall, in the past week, how much have you been bothered by these (PTSD SYMPTOMS) you've told me about? [Consider distress reported on earlier items]	0 *None* 1 *Mild, minimal distress* 2 *Moderate, distress clearly present but still manageable* 3 *Severe, considerable distress* 4 *Extreme, incapacitating distress*

24. Impairment in social functioning

In the past week, have these (PTSD SYMPTOMS) affected your relationships with other people? How so? [Consider impairment in social functioning reported on earlier items]	0 *No adverse impact* 1 *Mild impact, minimal impairment in social functioning* 2 *Moderate impact, definite impairment but many aspects of social functioning still intact* 3 *Severe impact, marked impairment, few aspects of social functioning still intact* 4 *Extreme impact, little or no social functioning*

25. Impairment in occupational or other important area of functioning

[If not clear:] **Are you working now?** [If yes:] **In the past week, have these (PTSD SYMPTOMS) affected your work or your ability to work? How so?** [If no:] **Why is that?** *(Do you feel that your [PTSD SYMPTOMS] are related to you not working now? How so?)* [If unable to work because of PTSD symptoms, rate at least 3=Severe. If unemployment is not due to PTSD symptoms, or if the link is not clear, base rating only on impairment in other important areas of functioning] **Have these (PTSD SYMPTOMS) affected any other important part of your life?** [As appropriate, suggest examples such as parenting, housework, schoolwork, volunteer work, etc.] **How so?**	0 *No adverse impact* 1 *Mild impact, minimal impairment in occupational/other important functioning* 2 *Moderate impact, definite impairment but many aspects of occupational/other important functioning still intact* 3 *Severe impact, marked impairment, few aspects of occupational/other important functioning still intact* 4 *Extreme impact, little or no occupational/other important functioning*

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Global Ratings

26. Global validity

Estimate the overall validity of responses. Consider factors such as compliance with the interview, mental status (e.g., problems with concentration, comprehension of items, dissociation), and evidence of efforts to exaggerate or minimize symptoms.	0	*Excellent, no reason to suspect invalid responses*
	1	*Good, factors present that may adversely affect validity*
	2	*Fair, factors present that definitely reduce validity*
	3	*Poor, substantially reduced validity*
	4	*Invalid responses, severely impaired mental status or possible deliberate "faking bad" or "faking good"*

27. Global severity

Estimate the overall severity of PTSD symptoms. Consider degree of subjective distress, degree of functional impairment, observations of behaviors in interview, and judgment regarding reporting style.	0	*No clinically significant symptoms, no distress and no functional impairment*
	1	*Mild, minimal distress or functional impairment*
	2	*Moderate, definite distress or functional impairment but functions satisfactorily with effort*
	3	*Severe, considerable distress or functional impairment, limited functioning even with effort*
	4	*Extreme, marked distress or marked impairment in two or more major areas of functioning*

28. Global improvement

Rate total overall improvement since the previous rating. Rate the degree of change, whether or not, in your judgment, it is due to treatment.	0	*Asymptomatic*
	1	*Considerable improvement*
	2	*Moderate improvement*
	3	*Slight improvement*
	4	*No improvement*
	5	*Insufficient information*

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Specify whether with dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

29. (1) Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

In the past week, have there been times when you felt as if you were separated from yourself, like you were watching yourself from the outside or observing your thoughts and feelings as if you were another person? [If no:] ***(What about feeling as if you were in a dream, even though you were awake? Feeling as if something about you wasn't real? Feeling as if time was moving more slowly?)*** **Tell me more about that.** **How strong is this feeling?** *(Do you lose track of where you actually are or what's actually going on?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme* [If not clear:] ***(Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?)*** [Rate 0=Absent if due to the effects of a substance or another medical condition] **How often has this happened in the past week?** *# of times*_____ **Did this feeling start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 1 X week / dissociative quality clearly present but transient, retains some realistic sense of self and awareness of environment Severe = at least 2 X week / pronounced dissociative quality, marked sense of detachment and unreality	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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30. (2) Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

In the past week, have there been times when things going on around you seemed unreal or very strange and unfamiliar? [If no:] ***(Do things going on around you seem like a dream or like a scene from a movie? Do they seem distant or distorted?)*** **Tell me more about that.** **How strong is this feeling?** *(Do you lose track of where you actually are or what's actually going on?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme* [If not clear:] ***(Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?)*** [Rate 0=Absent if due to the effects of a substance or another medical condition] **How often has this happened in the past week?** *# of times*_____ **Did this feeling start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 1 X week / dissociative quality clearly present but transient, retains some realistic sense of environment Severe = at least 2 X week / pronounced dissociative quality, marked sense of unreality	0 *Absent* 1 *Mild / subthreshold* 2 *Moderate / threshold* 3 *Severe / markedly elevated* 4 *Extreme / incapacitating*

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CAPS-5 SUMMARY SHEET

Name:_____ ID#:_____ Interviewer:_____ Study:_____ Date:_____

A. Exposure to actual or threatened death, serious injury, or sexual violence	
Criterion A met?	0 = NO 1 = YES

B. Intrusion symptoms (need 1 for diagnosis)	*Past Week*	
	Sev	*Sx (Sev ≥ 2)?*
(1) B1 – Intrusive memories		0 = NO 1 = YES
(2) B2 – Distressing dreams		0 = NO 1 = YES
(3) B3 – Dissociative reactions		0 = NO 1 = YES
(4) B4 – Cued psychological distress		0 = NO 1 = YES
(5) B5 – Cued physiological reactions		0 = NO 1 = YES
B subtotals	*B Sev =*	*# B Sx =*

C. Avoidance symptoms (need 1 for diagnosis)	*Past Week*	
	Sev	*Sx (Sev ≥ 2)?*
(6) C1 – Avoidance of memories, thoughts, feelings		0 = NO 1 = YES
(7) C2 – Avoidance of external reminders		0 = NO 1 = YES
C subtotals	*C Sev =*	*# C Sx =*

D. Cognitions and mood symptoms (need 2 for diagnosis)	*Past Week*	
	Sev	*Sx (Sev ≥ 2)?*
(8) D1 – Inability to recall important aspect of event		0 = NO 1 = YES
(9) D2 – Exaggerated negative beliefs or expectations		0 = NO 1 = YES
(10) D3 – Distorted cognitions leading to blame		0 = NO 1 = YES
(11) D4 – Persistent negative emotional state		0 = NO 1 = YES
(12) D5 – Diminished interest or participation in activities		0 = NO 1 = YES
(13) D6 – Detachment or estrangement from others		0 = NO 1 = YES
(14) D7 – Persistent inability to experience positive emotions		0 = NO 1 = YES
D subtotals	*D Sev =*	*# D Sx =*

E. Arousal and reactivity symptoms (need 2 for diagnosis)	*Past Week*	
	Sev	*Sx (Sev ≥ 2)?*
(15) E1 – Irritable behavior and angry outbursts		0 = NO 1 = YES
(16) E2 – Reckless or self-destructive behavior		0 = NO 1 = YES
(17) E3 – Hypervigilance		0 = NO 1 = YES
(18) E4 – Exaggerated startle response		0 = NO 1 = YES
(19) E5 – Problems with concentration		0 = NO 1 = YES
(20) E6 – Sleep disturbance		0 = NO 1 = YES
E subtotals	*E Sev =*	*# E Sx =*

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PTSD totals	*Past Week*	
	Total Sev	*Total # Sx*
Sum of subtotals (B+C+D+E)		

F. Duration of disturbance	*Current*
(22)	NOT APPLICABLE

G. Distress or impairment (need 1 for diagnosis)	*Past Week*	
	Sev	*Cx (Sev ≥ 2)?*
(23) Subjective distress		0 = NO 1 = YES
(24) Impairment in social functioning		0 = NO 1 = YES
(25) Impairment in occupational functioning		0 = NO 1 = YES
G subtotals	*G Sev =*	*# G Cx =*

Global ratings	*Past Week*
(26) Global validity	
(27) Global severity	
(28) Global improvement	

Dissociative symptoms (need 1 for subtype)	*Past Week*	
	Sev	*Sx (Sev ≥ 2)?*
(29) 1 – Depersonalization		0 = NO 1 = YES
(30) 2 – Derealization		0 = NO 1 = YES
Dissociative subtotals	*Diss Sev =*	*# Diss Sx =*

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Appendix 7 Symptoms of Trauma Scale (SOTS)

Chapter 3

Items, Definitions, and Anchoring Points
Symptoms of Trauma Scale (SOTS)

1. Re-experiencing

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Involuntary intrusion into present consciousness of memories or memory fragments (flashbacks) of past trauma; nightmares, intrusive memories, or feeling that one is reliving the traumatic experience.

1-Absent	Definition does not apply.
2-Minimal	Questionable pathology, may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) re-experiencing without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) re-experiencing without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) re-experiencing with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent re-experiencing cause distinct interference with day-to-day functioning and/or sometimes exceed the persons ability to cope/manage.
6-Severe	Frequent re-experiencing cause severe interference with day to day functioning and/or often exceed ability to cope/manage, but do not lead to a life-threatening situation to self or others
7-Extreme	Frequent re-experiencing cause complete interference with day-to-day functioning and/or completely override ability to cope/manage and/or lead to a life-threatening situation to self or others

2. Hyperarousal

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Hyperarousal, hypervigilance, increased reactivity or exaggerated startle response.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) hyperarousal, without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) hyperarousal without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) hyperarousal with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully
5-Moderate/ Severe	Frequent hyperarousal causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent hyperarousal causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others
7-Extreme	Frequent hyperarousal causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others

3. Affective Dysregulation

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Emotions are experienced as overwhelming, too changeable, ego dystonic, or too extreme to be tolerable (Does not include episodes that qualify for DSM bipolar disorder manic episodes).

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) affective dysregulation, without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) affective dysregulation without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) affective dysregulation with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent affective dysregulation causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent affective dysregulation causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others.
7-Extreme	Frequent affective dysregulation causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others

4. Impulsivity

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Inability to regulate, control or manage intense affect that becomes apparent in verbalizing or acting out feelings impulsively, or in potentially dangerous ways (such as self-injury, aggression/assaultiveness, or behaviors that are high-risk or addictive).

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) impulsive behavior, without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) impulsive behavior without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) impulsive behavior with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent impulsive behavior causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent impulsive behavior causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others.
7-Extreme	Frequent impulsive behavior causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others

5. Avoidance

Past Week: ____ (If not the past week, specify time frame)

Note: If also assessing **lifetime**, circle present or absent below

Lifetime: present or absent (circle one)

Definition: Avoiding people, places, things, activities, thoughts or conversations related to trauma.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) avoidance, without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) avoidance without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) avoidance with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent avoidance causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent avoidance causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others
7-Extreme	Frequent avoidance causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others.

6. Numbing

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Inability or decreased ability to experience a full range of feelings.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) numbing, without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) numbing without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) numbing with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent numbing causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent numbing causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others
7-Extreme	Frequent numbing causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others

7. Attention/Consciousness/Dissociation

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Split in present consciousness or partial unawareness/blocking out from present consciousness: depersonalization, derealization, periods of 'losing time' (amnesia, fugue, shifting into different identities/personalities without awareness).

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) dissociation, without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) dissociation without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) dissociation with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent dissociation causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent dissociation causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others
7-Extreme	Frequent dissociation causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others

8. Self Perception

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Feeling damaged, ashamed, guilty or blaming self for past trauma. Can be angry at self for lack of ability to stop traumatic event.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits
3-Mild	Infrequently (twice or less/week) feeling damaged, ashamed, guilty or blaming self for past trauma without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequently (more than twice a week) feeling damaged, ashamed, guilty or blaming self for past trauma without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequently (twice or less/week) feeling damaged, ashamed, guilty or blaming self for past trauma with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequently feeling damaged, ashamed, guilty or blaming self for past trauma causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage
6-Severe	Frequently feeling damaged, ashamed, guilty or blaming self for past trauma causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others
7-Extreme	Frequently feeling damaged, ashamed, guilty or blaming self for past trauma causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others.

9. Interpersonal Relations

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Lack of trust in other people and/or problems with relating and boundaries. Relationships are intense, enmeshed, intrusive and/or unstable, **or** the person is isolated and/or disconnected from others.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) lack of trust in other people and/or problems with relating and boundaries without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) lack of trust in other people and/or problems with relating and boundaries without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) lack of trust in other people and/or problems with relating and boundaries with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent lack of trust in other people and/or problems with relating and boundaries cause distinct interference with day-to-day functioning and/or sometimes exceed the persons ability to cope/manage.
6-Severe	Frequent lack of trust in other people and/or problems with relating and boundaries cause severe interference with day to day functioning and/or often exceed ability to cope/manage, but do not lead to a life-threatening situation to self or others
7-Extreme	Frequent lack of trust in other people and/or problems with relating and boundaries cause complete interference with day-to-day functioning and/or completely override ability to cope/manage and/or lead to a life-threatening situation to self or others.

10. Alterations in Sexual Relations/Behaviors

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Changes in sexual thoughts, feelings, behaviors or relations, including hypersexuality (sex addiction, promiscuity, sexually high risk behaviors) or extreme disinterest in sexuality or absence of sexual feelings and/or avoidance of sexuality/physical touch.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) alterations in sexual relations/behaviors without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) alterations in sexual relations/behaviors without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) alterations in sexual relations/behaviors with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent alterations in sexual relations/behaviors cause distinct interference with day-to-day functioning and/or sometimes exceed the persons ability to cope/manage.
6-Severe	Frequent alterations in sexual relations/behaviors cause severe interference with day to day functioning and/or often exceed ability to cope/manage, but do not lead to a life-threatening situation to self or others
7-Extreme	Frequent alterations in sexual relations/behaviors cause complete interference with day-to-day functioning and/or completely override ability to cope/manage and/or lead to a life-threatening situation to self or others.

11. Sustaining Beliefs

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Loss of faith, meaning or sustaining beliefs, and/or feeling purposeless.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3-Mild	Infrequent (twice or less/week) loss of faith, meaning or sustaining beliefs without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) loss of faith, meaning or sustaining beliefs without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) loss of faith, meaning or sustaining beliefs with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate/ Severe	Frequent loss of faith, meaning or sustaining beliefs cause distinct interference with day-to-day functioning and/or sometimes exceed the persons ability to cope/manage.
6-Severe	Frequent loss of faith, meaning or sustaining beliefs cause severe interference with day to day functioning and/or often exceed ability to cope/manage, but do not lead to a life-threatening situation to self or others
7-Extreme	Frequent loss of faith, meaning or sustaining beliefs cause complete interference with day-to-day functioning and/or completely override ability to cope/manage and/or lead to a life-threatening situation to self or others.

12. Somatic Dysregulation

Past Week: ____ (If not the past week, specify time frame)

Lifetime: present or absent (circle one)

Definition: Physical health problems that are more extensive or severe than can be attributed to a physical illness or medical condition or that are exacerbated more than expected by current stressors. For example, extreme bodily pain or fatigue, or severe GI, respiratory, cardiovascular, genito-urinary, inflammatory, or auto-immune health problems.

1-Absent	Definition does not apply
2-Minimal	Questionable pathology; may be at the upper extreme of normal limits
3-Mild	Infrequent (twice or less/week) somatic dysregulation without significant psychological distress or physiological reactivity. Does not cause any interference in day-to-day functioning.
4-Moderate	Either (a) frequent (more than twice a week) somatic dysregulation without significant psychological distress or physiological reactivity or interference in daily activities and the person is able to cope/manage successfully; or (b) infrequent (twice or less/week) somatic dysregulation with significant psychological distress or physiological reactivity that cause some interference with day-to-day functioning but the person is able to cope/manage successfully.
5-Moderate Severe	Frequent somatic dysregulation causes distinct interference with day-to-day functioning and/or sometimes exceeds the persons ability to cope/manage.
6-Severe	Frequent somatic dysregulation causes severe interference with day to day functioning and/or often exceeds ability to cope/manage, but does not lead to a life-threatening situation to self or others
7-Extreme	Frequent somatic dysregulation causes complete interference with day-to-day functioning and/or completely overrides ability to cope/manage and/or leads to a life-threatening situation to self or others.

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13. Data on Symptoms in General

13.1) When did symptoms in general first begin? _____

13.2) When were these symptoms at their worst?
_____

13.3) How does this compare to the past week?

___worse
___same
___better

13.4) What kinds of circumstances increase the intensity of these symptoms?
_____
_____

13.5) Does the severity fluctuate with everyday stressors not related to the trauma?
_____

13.6) Does the severity of your symptoms fluctuate with mood changes not related to everyday stressors?
_____
_____

13.7) Of the symptoms we discussed, which ones have been most disabling?
_____
_____

13.8) How about during the past week? _____
_____

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Chapter 4

Structured Clinical Interview for the Symptoms of Trauma Scale (SCI-SOTS)

Instructions to interviewer:

The SCI-SOTS is being administered to assess the presence and severity of trauma symptoms. The SCI-SOTS should be administered after you have had a chance to familiarize yourself with a previously obtained trauma history. The SCI-SOTS asks about symptom severity in the previous week as well as anytime in the past. The questions below can be asked as written, if appropriate, but most of the time should be paraphrased to be syntonic with the setting and people being interviewed. The order of the questions can also be modified as long as all information on every question is obtained. You may incorporate the patient's specific trauma in place of the generic wording "traumatic experience/s."

While the interview does not revisit the traumatic event(s), if the interviewee feels that he/she needs to share some information about his/her traumatic experience/(s), use clinical judgment as regards the pros and cons.

Throughout the administration of the interview it is extremely important to respect the subject's sensibilities and boundaries and maintain an empathic stance. If the person declines to answer a question when you first ask, you may want to ask if you could revisit that question later.

Start the interview by saying the following:

"Hello...my name is _____ and I'm going to be asking you questions about some symptoms that you may have experienced or are experiencing currently. The symptoms I'll be asking you about are related to traumatic experiences that you may have experienced in the past. I will not be asking you details about your trauma history, but rather about how it has affected you. However, if you feel that you need to share some information about your history in order to answer a question, that's fine.
I will be asking about a lot of symptoms, but if it feels that I am moving too quickly, please let me know. Also, if some of the questions stir up difficult feelings let me know when you are feeling uncomfortable or having a hard time.

I want to better understand how each symptom affects you, so I have to ask similar questions about each symptom, which might feel repetitive at times. If any of the words I use or questions I ask are unclear, please ask me to explain. If at any time during the interview you feel uncomfortable, please let me know. By the way, I may make some notes during the interview. Do you have any questions for me before we begin?"

Item 1: Data on Reexperiencing

Definition: Involuntary intrusion into present consciousness of memories or memory fragments (flashbacks) of past trauma; nightmares, intrusive memories, or feeling that one is reliving the traumatic experience.

1:1) Do you sometimes feel that you are reliving a past traumatic experience, or have intrusive memories, flashbacks, or nightmares related to trauma in the past?

1.2) How about in the past week?

1:3) How did this affect you? Emotionally? Physically? (**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart

racing)

1:4) In the past week how often has this occurred?

1:5) Has this (reliving a past traumatic experience or intrusive memories or flashbacks or nightmares) ever interfered with your daily activities or your ability to function?

1:6) In what way has this interfered with your daily activities or your ability to function?

1:7) How about in the past week?

1:8) When an unwanted memory or distressing reminder causes you to relive the past trauma, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

1:9) How about in the past week?

1:10) Has your having an unwanted memory or distressing reminder of the trauma put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

1:11) Has this occurred in the past week?

Item 2: Data on Hyperarousal

Definition: Hyperarousal, hypervigilance, increased reactivity or exaggerated startle response.

2:1) Do you sometimes feel extremely tense, irritable, jumpy, on guard, or easily startled?

2:1a) If no, proceed to item 3

2:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

2:2) How about in the past week?

2:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:**Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

2:4) In the past week how often has this occurred?

2:5) Have any of these difficulties (sometimes feel extremely tense, irritable, jumpy, on guard, or easily startled) ever interfered with your daily activities or your ability to function?

2:6) In what way do they interfere with your daily activities or ability to function?

2:7) How about in the past week?

2:8) When you feel extremely tense, irritable, jumpy, on guard, or easily startled, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

2:9) How about in the past week?

2:10) Has your feeling extremely tense, irritable, jumpy, on guard, or easily startled ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

2:11) Has this occurred in the past week?

Item 3: Data on Affective Dysregulation

Definition: Emotions are experienced as overwhelming, too changeable, egodystonic, or too extreme to be tolerable (Does not include episodes that qualify for DSM bipolar disorder manic episodes).

3:1) Do you ever have difficulties controlling your moods? For example, because of the past trauma, does your mood become overwhelming and out of control at times and/or do you experience mood swings and/or have you had intense feelings of anger, sadness, fear or rage?

3:1a) If no, proceed to item 4

3:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

3:2) How about in the past week?

3:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:**Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

3:4) In the past week how often has this occurred?

3:5) Have any of these difficulties (mood seeming out of control, experiencing mood swings, or having intense feelings of anger, sadness, fear or rage) ever interfered with your daily activities or your ability to function?

3:6) In what way do they interfere with your daily activities or ability to function?

3:7) How about in the past week?

3:8) When you experience mood swings, or have intense feelings of anger, sadness, fear or rage, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

3:9) How about in the past week?

3:10) Have your mood swings, or intense feelings of anger, sadness, fear or rage ever put you or someone else in danger? (**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

3:11) Has this occurred in the past week?

Item 4: Data on Impulse Control

Definition: Inability to regulate, control or manage intense affect that becomes apparent in verbalizing or acting out feelings impulsively, or in potentially dangerous ways (such as self-injury, aggression/assaultiveness, or behaviors that are high-risk or addictive).

4:1) As a result of the past trauma, have you ever had trouble with controlling your impulses or risk taking behaviors? This may include behaviors such as drinking too much or using drugs, driving recklessly or making risky sexual choices, or acting destructively, including self-destructively.

4:1a) If no, proceed to item 5

4:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

4:2) How about in the past week?

4:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

4:4) In the past week how often has this occurred?

4:5) Have any of these difficulties (trouble with controlling your impulses or risk taking behaviors) ever interfered with your daily activities or your ability to function?

4:6) In what way do they interfere with your daily activities or ability to function?

4:7) How about in the past week?

4:8) When you experience trouble with controlling your impulses or risk taking behaviors, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

4:9) How about in the past week?

4:10) Have your trouble with controlling your impulses or risk taking behaviors, ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

4:11) Has this occurred in the past week?

Item 5: Data on Avoidance

Definition: Avoiding people, places, things, activities, conversations or thoughts related to trauma.

5:1) As a result of past trauma have you ever found yourself avoiding certain thoughts or situations such as places, people, or things that remind you of the traumatic experience?

5:1a) If no, proceed to item 6

5:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

5:2) How about in the past week?

5:3) How did this affect you?

5:4) In the past week how often has this occurred?

5:5) Have any of these difficulties (avoiding certain thoughts or situations such as places, people, or things) ever interfered with your daily activities or your ability to function?

5:6) In what way do they interfere with your daily activities or ability to function?

5:7) How about in the past week?

5:8) When you experience avoiding certain thoughts or situations such as places, people, or things, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

5:9) How about in the past week?

5:10) Has your avoiding certain thoughts or situations such as places, people, or things ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

5:11) Has this occurred in the past week?

Item 6: Data on Numbing

Definition: Inability or decreased ability to experience a full range of feelings.

6:1) Sometimes people who have survived a trauma describe feeling numb or being unable to feel. Have you ever experienced feeling numb or thought that your feelings were blunted, or that you had no feelings at all?

6:1a) If no, proceed to item 7

6:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

6:2) How about in the past week?

6:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:**Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

6:4) In the past week how often has this occurred?

6:5) Have any of these difficulties (feeling numb or being unable to feel) ever interfered with your daily activities or your ability to function?

6:6) In what way do they interfere with your daily activities or ability to function?

6:7) How about in the past week?

6:8) When you experience numbness or are unable to feel, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

6:9) How about in the past week?

6:10) Have your feelings of numbness ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

6:11) Has this occurred in the past week?

Item 7: Data on Dissociation

Definition: Split in present consciousness or partial unawareness or blocking out from present consciousness: depersonalization, derealization, periods of 'losing time' (amnesia, fugue, shifting into different identities/personalities without awareness).

7:1) Have you ever felt "spaced out," or felt as though you were "outside your body" observing your life as it happens or as though events were not real or not really happening to you? Have you lost your memory

for a period of time, so that you couldn't remember what you had done, or found yourself in a place without knowing how you got there?

7:1a) If no, proceed to item 8

7:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

7:2) How about in the past week?

7:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

7:4) In the past week how often has this occurred?

7:5) Have any of these difficulties (feeling "spaced out") ever interfered with your daily activities or your ability to function?

7:6) In what way do they interfere with your daily activities or ability to function?

7:7) How about in the past week?

7:8) When you feel "spaced out", what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

7:9) How about in the past week?

7:10) Has feeling "spaced out" ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

7:11) Has this occurred in the past week?

Item 8: Data on Alteration in Self-Perception

Definition: Feeling damaged, ashamed, guilty or blaming self for past trauma. Can be angry at self for lack of ability to stop traumatic event.

8:1) After a traumatic experience some people feel differently about themselves (e.g. guilty, ashamed, damaged or dirty, worthy of mistreatment, feeling singled out for victimization, or feeling responsible for what happened). Have you ever had any of these feelings?

8:1a) If no, proceed to item 9

8:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

8:2) How about in the past week?

8:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

8:4) In the past week how often has this occurred?

8:5) Has feeling differently ever interfered with your daily activities or your ability to function?

8:6) In what way does it interfere with your daily activities or ability to function?

8:7) How about in the past week?

8:8) When you experience feeling differently, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

8:9) How about in the past week?

8:10) Have your feeling differently ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

8:11) Has this occurred in the past week?

Item 9: Data on Alteration in Interpersonal Relations

Definition: Lack of trust in other people and/or problems with relating and boundaries. Relationships are intense, enmeshed, intrusive and/or unstable, or the person is isolated and/or disconnected from others.

9:1) Sometimes people who've experienced a trauma have difficulties in their relationships with other people. For example, they may have trouble trusting or relating to others. They may have difficulties with closeness, either feeling isolated and distant from others, or getting too close too fast. They may have frequent conflicts, arguments or misunderstandings with others, or end relationships abruptly. Have you ever had any such difficulties?

9:1a) If no, proceed to item 10

9:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

9:2) How about in the past week?

9:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and

physical symptoms (e.g. shaking, sweating, heart racing)

9:4) In the past week how often has this occurred?

9:5) Have any of these difficulties in relationships ever interfered with your daily activities or your ability to function?

9:6) In what way do they interfere with your daily activities or ability to function?

9:7) How about in the past week?

9:8) When you have difficulties in relationships, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

9:9) How about in the past week?

9:10) Have those difficulties in relationships ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

9:11) Has this occurred in the past week?

Item 10: Data on Alterations in Sexual Relations or Behavior

Definition: Changes in sexual thoughts, feelings, behaviors or relations, including hypersexuality (sex addiction, promiscuity, sexually high risk behaviors) or extreme disinterest in sexuality or absence of sexual feelings and/or avoidance of sexuality/physical touch.

10:1) Sometimes people who have experienced trauma feel distressed or disgusted by sex, or feel the need to avoid sexual relationships entirely. Others have difficulty negotiating their needs in a sexual relationship. Alternatively they may feel preoccupied by or addicted to sex or not know how to handle sexuality within relationships. Have you ever had any of these feelings?

10:1a) If no, proceed to item 11

10:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

10:2) How about in the past week?

10:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

10:4) In the past week how often has this occurred?

10:5) Have these feelings or behaviors ever interfered with your daily activities or your ability to function?

10:6) In what way does it interfere with your daily activities or ability to function?

10:7) How about in the past week?

10:8) When you experience these feelings or behaviors, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

10:9) How about in the past week?

10:10) Have these feelings or behaviors ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

10:11) Has this occurred in the past week?

Item 11: Data on Loss of Sustaining Beliefs

Definition: Loss of faith, meaning or sustaining beliefs, and/or feeling purposeless.

11:1) After experiencing a trauma some people lose faith in beliefs that used to be important to them, or feel that their life has no purpose or meaning. Have you ever felt like this?

11:1a) If no, proceed to item 12

11:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

11:2) How about in the past week?

11:3) How did this affect you? Emotionally? Physically? (**Instruction to interviewer:** Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

11:4) In the past week how often has this occurred?

11:5) Has losing faith in beliefs or that life has no purpose ever interfered with your daily activities or your ability to function?

11:6) In what way do they interfere with your daily activities or ability to function?

11:7) How about in the past week?

11:8) When you lose faith or feel that life has no purpose, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

11:9) How about in the past week?

11:10) Has losing faith in beliefs or feeling that life has no purpose ever put you or someone else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

11:11) Has this occurred in the past week?

Item 12: Data on Bodily Manifestations of Trauma

Definition: Physical health problems that are more extensive or severe than can be attributed to a physical illness or medical condition or that are exacerbated more than expected by current stressors. For example, extreme bodily pain or fatigue, or severe GI, respiratory, cardiovascular, genito-urinary, inflammatory, or auto-immune health problems.

12:1) Have you ever experienced any physical symptoms or illness for which no medical basis can be found? If so, what are your symptoms?

12:1a) If no, proceed to **Part 2: Data on Symptoms in General**

12:1b) If yes, ask "Is this related to past trauma?" (As the SOTS is NOT a self report instrument, the rater may disagree with subject regarding relationship of symptom to past trauma: if this is the case, provide a brief written explanation, e.g. on the rating form)

12:2) How about in the past week?

12:3) How did this affect you? Emotionally? Physically?

(**Instruction to interviewer:**Probe for emotional symptoms (e.g. feeling afraid, sad, upset or angry) and physical symptoms (e.g. shaking, sweating, heart racing)

12:4) In the past week how often has this occurred?

12:5) Have those any physical symptoms ever interfered with your daily activities or your ability to function?

12:6) In what way do they intertere with your daily activities or ability to function?

12:7) How about in the past week?

12:8) When you experience those physical symptoms, what has helped you cope?

(**Instruction to interviewer:** Probe for the following coping mechanisms/techniques: remembering that the trauma is not happening now; calming body and emotions; making a practical plan that helps the subject feel in control, safe, and hopeful.)

12:9) How about in the past week?

12:10) Has experiencing those physical symptoms ever put you or someore else in danger?

(**Instruction to interviewer:** If yes, probe for seriousness, and, in particular, dangerousness to self or others)

12:11) Has this occurred in the past week?

Part 2: Data on Symptoms in General

(**Instruction to interviewer:** Say the following to interviewee:)

Now I would like to ask you about these trauma related symptoms in general.

In general:

13:1) When did these symptoms first begin?

13:2) When were these symptoms at their worst?

13:3) How does this compare to the past week?

13:4) What kinds of circumstances increase the intensity of these symptoms?

13:5) Does the severity fluctuate with everyday stressors not related to the trauma?

13:6) Does the severity of your symptoms fluctuate with mood changes not related to everyday stressors?

13:7) Of the symptoms we discussed, which ones have been most disabling?

13:8) How about during the past week?

(**Instruction to interviewer: CONCLUDE INTERVIEW WITH A DEBRIEFING SESSION.** Say the following to interviewee:)

This concludes our interview. Thank you for participating. How do you feel right now? How did you feel during the interview? Do you have any questions? Is there anything you would like to talk about that is related to the interview but we haven't discussed? (If indicated) Are you safe to leave the interview? Thank you!

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Appendix 8 Clinical Global Impression - Severity (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

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Appendix 9 PTSD Checklist for DSM-5 (PCL-5)

PCL-5 with Criterion A

Instructions: This questionnaire asks about problems you may have had after a very stressful experience involving actual or threatened death, serious injury, or sexual violence. It could be something that happened to you directly, something you witnessed, or something you learned happened to a close family member or close friend. Some examples are a serious accident; fire; disaster such as a hurricane, tornado, or earthquake; physical or sexual attack or abuse; war; homicide; or suicide.

First, please answer a few questions about your worst event, which for this questionnaire means the event that currently bothers you the most. This could be one of the examples above or some other very stressful experience. Also, it could be a single event (for example, a car crash) or multiple similar events (for example, multiple stressful events in a war-zone or repeated sexual abuse).

Briefly identify the worst event (if you feel comfortable doing so):

_____

_____

_____

_____

How long ago did it happen? _____ (please estimate if you are not sure)

Did it involve actual or threatened death, serious injury, or sexual violence?

_____ Yes

_____ No

How did you experience it?

_____ It happened to me directly

_____ I witnessed it

_____ I learned about it happening to a close family member or close friend

_____ I was repeatedly exposed to details about it as part of my job (for example, paramedic, police, military, or other first responder)

_____ Other, please describe _____

If the event involved the death of a close family member or close friend, was it due to some kind of accident or violence, or was it due to natural causes?

_____ Accident or violence

_____ Natural causes

_____ Not applicable (the event did not involve the death of a close family member or close friend)

PCL-5 with Criterion A (14 August 2013) National Center for PTSD Page 1 of 2

Second, below is a list of problems that people sometimes have in response to a very stressful experience. Keeping your worst event in mind, please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13. Feeling distant or cut off from other people?	0	1	2	3	4
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17. Being "superalert" or watchful or on guard?	0	1	2	3	4
18. Feeling jumpy or easily startled?	0	1	2	3	4
19. Having difficulty concentrating?	0	1	2	3	4
20. Trouble falling or staying asleep?	0	1	2	3	4

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Appendix 10 Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**	**I feel as if I am slowed down:**	**D**
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
I still enjoy the things I used to enjoy:	**D**	**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
I get a sort of frightened feeling like something awful is about to happen:	**A**	**I have lost interest in my appearance:**	**D**
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
I can laugh and see the funny side of things:	**D**	**I feel restless as if I have to be on the move:**	**A**
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
Worrying thoughts go through my mind:	**A**	**I look forward with enjoyment to things:**	**D**
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2
I feel cheerful:	**D**	**I get sudden feelings of panic:**	**A**
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
I can sit at ease and feel relaxed:	**A**	**I can enjoy a good book or radio or TV programme:**	**D**
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

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Appendix 11 Emory Treatment Resistance Interview for PTSD (E-TRIP)

E-TRIP [EMORY TREATMENT RESISTANCE INTERVIEW FOR PTSD]

OVERVIEW

- Start the E-TRIP assessment by handing the **PTSD Medication Treatment Record** and **PTSD Psychotherapy Treatment Record** pages to the patient. The patient should indicate the treatments they have previously received by marking the check boxes next to the treatments. Advise the patient that their only action on the form is to check the boxes in the white (unshaded) areas; they should ignore the rest of the form (these areas can also be covered so as not to confuse patients completing the form).
- Medications are grouped by classes for ease of organization, and antipsychotics are included in "other agents" to avoid the possible misinterpretation that they may only be used for patients with psychotic symptoms. For each efficacious psychotherapy, a single sentence description is provided to help patients who may not have been told the specific name of the psychotherapy they received.
- After the patient has completed the Treatment Records, the interviewer collects them and administers the semi-structured interview.
- Questions in **Bold** font should be asked as written.
- Text within boxes provides instructions to the interviewer for how to proceed and how to mark the Treatment Record.
- Each shaded gray box (for instance, Start Date MM/YYYY) indicates with which column on the Treatment Record the instruction corresponds.
- The interview begins by assessing the onset of PTSD and primary symptoms; if this information is already known, these questions do not need to be asked, although the relevant information should be recorded. Identifying onset of PTSD is crucial for determining treatment resistance, because many patients who had episodes of anxiety or depression before experiencing a trauma may record on the treatment records that they had received specific treatments, though in fact those treatments were administered prior to the onset of PTSD and therefore should not contribute to the E-TRIP score.
- Next, the interviewer evaluates the response to the individual treatments. The interview has separate sections for medication and psychotherapy treatments. For each individual treatment for which the patient has checked the box, the interviewer proceeds through the interview, one treatment at a time, following the instructions and recording answers in the Treatment Record. For instance, if a patient had been treated with sertraline and venlafaxine, the interviewer would ask questions 3-5 in regards to sertraline, then return to question 3 and assess venlafaxine. This applies to psychotherapy treatments as well.

NOTE: For psychotherapy and medication treatments administered concomitantly, the key consideration is whether the patient responded while receiving the treatments. If so, no points for resistance will be scored. If the patient did not respond, then points should be scored for both treatments, just as if they had been administered separately.

PATIENT ID: **DATE:** **INTERVIEWER:**

E-TRIP PTSD MEDICATION TREATMENT RECORD

Have you ever taken a prescription medication for PTSD? ☐ No ☐ Yes
If yes, please review the list of medications below and check the box (☐) next to any you have taken in the past or are taking now.
DO NOT WRITE IN THE GRAY-SHADED AREAS

PATIENT SECTION			OFFICE USE ONLY								
Generic name	Trade name	Check box if ever taken	Start date MM/YYYY	For PTSD?	Dose used	Minimum effective dose	Used to augment?	≥ 8 weeks?	≥6 days/ week?	If adequate trial, responded?	Points†
SSRIs											
Citalopram	Celexa	☐		Y N		20 mg/d	Y N	Y N	Y N	Y N U	3
Escitalopram	Lexapro	☐		Y N		10 mg/d	Y N	Y N	Y N	Y N U	3
Fluoxetine	Prozac	☐		Y N		20 mg/d	Y N	Y N	Y N	Y N U	3
Fluvoxamine	Luvox	☐		Y N		50 mg/d	Y N	Y N	Y N	Y N U	3
Paroxetine	Paxil (Paxil CR)	☐		Y N		20 mg/d (25)	Y N	Y N	Y N	Y N U	3
Sertraline	Zoloft	☐		Y N		50 mg/d	Y N	Y N	Y N	Y N U	3
Vilazodone	Viibryd	☐		Y N		20 mg/d	Y N	Y N	Y N	Y N U	3
SNRIs											
Desvenlafaxine	Pristiq	☐		Y N		50 mg/d	Y N	Y N	Y N	Y N U	0
Duloxetine	Cymbalta	☐		Y N		40 mg/d	Y N	Y N	Y N	Y N U	0
Venlafaxine	Effexor	☐		Y N		75 mg/d	Y N	Y N	Y N	Y N U	3
TCAs											
Amitriptyline	Elavil	☐		Y N		150 mg/d	Y N	Y N	Y N	Y N U	0
Clomipramine	Anafranil	☐		Y N		150 mg/d	Y N	Y N	Y N	Y N U	0
Desipramine	Norpramin	☐		Y N		150 mg/d	Y N	Y N	Y N	Y N U	0
Doxepin	Sinequan	☐		Y N		150 mg/d	Y N	Y N	Y N	Y N U	0
Imipramine	Tofranil	☐		Y N		150 mg/d	Y N	Y N	Y N	Y N U	2
Nortriptyline	Pamelor	☐		Y N		75 mg/d	Y N	Y N	Y N	Y N U	0
MAOIs											
Phenelzine	Nardil	☐		Y N		45 mg/d	Y N	Y N	Y N	Y N U	2
Selegiline	Emsam	☐		Y N		6 mg/24 hrs	Y N	Y N	Y N	Y N U	0
Tranylcypromine	Parnate	☐		Y N		30 mg/d	Y N	Y N	Y N	Y N U	0
OTHER ANTIDEPRESSANTS											
Bupropion	Wellbutrin	☐		Y N		300 mg/d	Y N	Y N	Y N	Y N U	0
Mirtazapine	Remeron	☐		Y N		30 mg/d	Y N	Y N	Y N	Y N U	0
Nefazodone	Serzone	☐		Y N		300 mg/d	Y N	Y N	Y N	Y N U	2
Trazodone	Desyrel	☐		Y N		300 mg/d	Y N	Y N	Y N	Y N U	0

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E-TRIP PTSD MEDICATION TREATMENT RECORD

PATIENT SECTION			OFFICE USE ONLY								
Generic name	Trade name	Check box if ever taken	Start date MM/YYYY	For PTSD?	Dose used	Minimum effective dose	Used to augment?	≥8 weeks?	≥6 days/ week?	If adequate trial, responded? (Y, N, U)	Points?
BENZODIAZEPINES/SEDATIVES											
Clonazepam	Klonopin	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Lorazepam	Ativan	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Alprazolam	Xanax	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Diazepam	Valium	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Eszopiclone	Lunesta	☐		Y N		3 mg/d	Y N	*Y N	Y N	Y N U	1
Zolpidem	Ambien	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Zaleplon	Sonata	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
OTHER MEDICATIONS											
Aripiprazole	Abilify	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Olanzapine	Zyprexa	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Quetiapine	Seroquel	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Risperidone	Risperdal	☐		Y N		2 mg/d	Y N	Y N	Y N	Y N U	1
Prazosin	Minipress	☐		Y N		3 mg/d	Y N	Y N	Y N	Y N U	1
Lamotrigine	Lamictal	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Levetiracetam	Keppra	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Topiramate	Topamax	☐		Y N		100 mg/d	Y N	Y N	Y N	Y N U	1
Valproic Acid	Depakote	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Gabapentin	Neurontin	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Pregabalin	Lyrica	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Carbamazepine	Tegretol	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Clonidine	Catapres	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Guanfacine	Tenex	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Propranolol	Inderal	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
Atenolol	Tenormin	☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
UNLISTED (Write in below)											
		☐		Y N		n/a	Y N	Y N	Y N	Y N U	0
		☐		Y N		n/a	Y N	Y N	Y N	Y N U	0

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* When eszopiclone is used for augmentation, ≥3 weeks constitutes an adequate trial; 8 weeks is not required.

MEDICATION TOTAL POINTS: _____

PATIENT ID: DATE: INTERVIEWER:

E-TRIP PTSD PSYCHOTHERAPY TREATMENT RECORD

Have you ever received psychotherapy (talk therapy) for the treatment of PTSD? ☐ **No** ☐ **Yes**

If yes, please review the list of therapies below and check any you have received in the past or are receiving now. If you are unclear about the name of the therapy you have received, use the descriptions to identify which seems most like the treatment you received.

DO NOT WRITE IN THE GRAY-SHADED AREAS

PATIENT SECTION		OFFICE USE ONLY					
Form of Psychotherapy	Check box if you received	Start date MM/YYYY	For PTSD?	No. of Sessions	Minimum No. of Sessions	If adequate trial, responded?	Points
TRAUMA-FOCUSED CBT							
Prolonged Exposure (PE): You repeatedly went over the memory of the traumatic event by saying it out aloud with the therapist, and possibly by listening to a recording of you saying it while at home.	☐		Y N		6	Y N U	3
Cognitive Processing Therapy (CPT): You talked with the therapist about the "stuck points" that were the aspects of the event that were the most emotionally upsetting to you.	☐		Y N		6	Y N U	3
Eye Movement Desensitization and Reprocessing (EMDR): You went through the memory of the traumatic event while doing something repetitive, like following the therapist's finger from side to side with your eyes.	☐		Y N		6	Y N U	2
Trauma-Focused Cognitive-Behavioral Therapy (TFCBT): You discussed thoughts about the trauma with the therapist and were assigned homework. You described the trauma aloud to the therapist.	☐		Y N		6	Y N U	3
Narrative Exposure Therapy (NET): You described the story of your life to the therapist and all emotions that went along with the events in your life.	☐		Y N		6	Y N U	2
Written Exposure Therapy (WET): You were asked to write a detailed account of your trauma in each session, emphasizing sounds and images as well as thoughts and emotions at the time of the trauma.	☐		Y N		5	Y N U	2
Cognitive Restructuring: You identified unhelpful beliefs you have and worked with the therapist to change those beliefs by examining the evidence for and against the beliefs.	☐		Y N		6	Y N U	0
Stress Inoculation Therapy (SIT): You learned coping skills to manage anxiety related to the trauma including tools to change unhelpful thoughts, relaxation exercises, and guided self-talk.	☐		Y N		6	Y N U	0
Dialectical Behavior Therapy for PTSD: You learned skills such as emotion regulation and distress tolerance and acceptance.	☐		Y N		6	Y N U	2
Nightmare Imagery Rehearsal/CBT: You were asked to write down a nightmare related to the trauma. You then altered the nightmare into a more positive story and rehearsed this repeatedly.	☐		Y N		6	Y N U	0
INTERNET-BASED THERAPIES							
Internet-based Cognitive-Behavioral Therapy: You used a website to communicate with a therapist and complete assignments. You wrote about your trauma and learned to share your experience with others.	☐		Y N		6	Y N U	3

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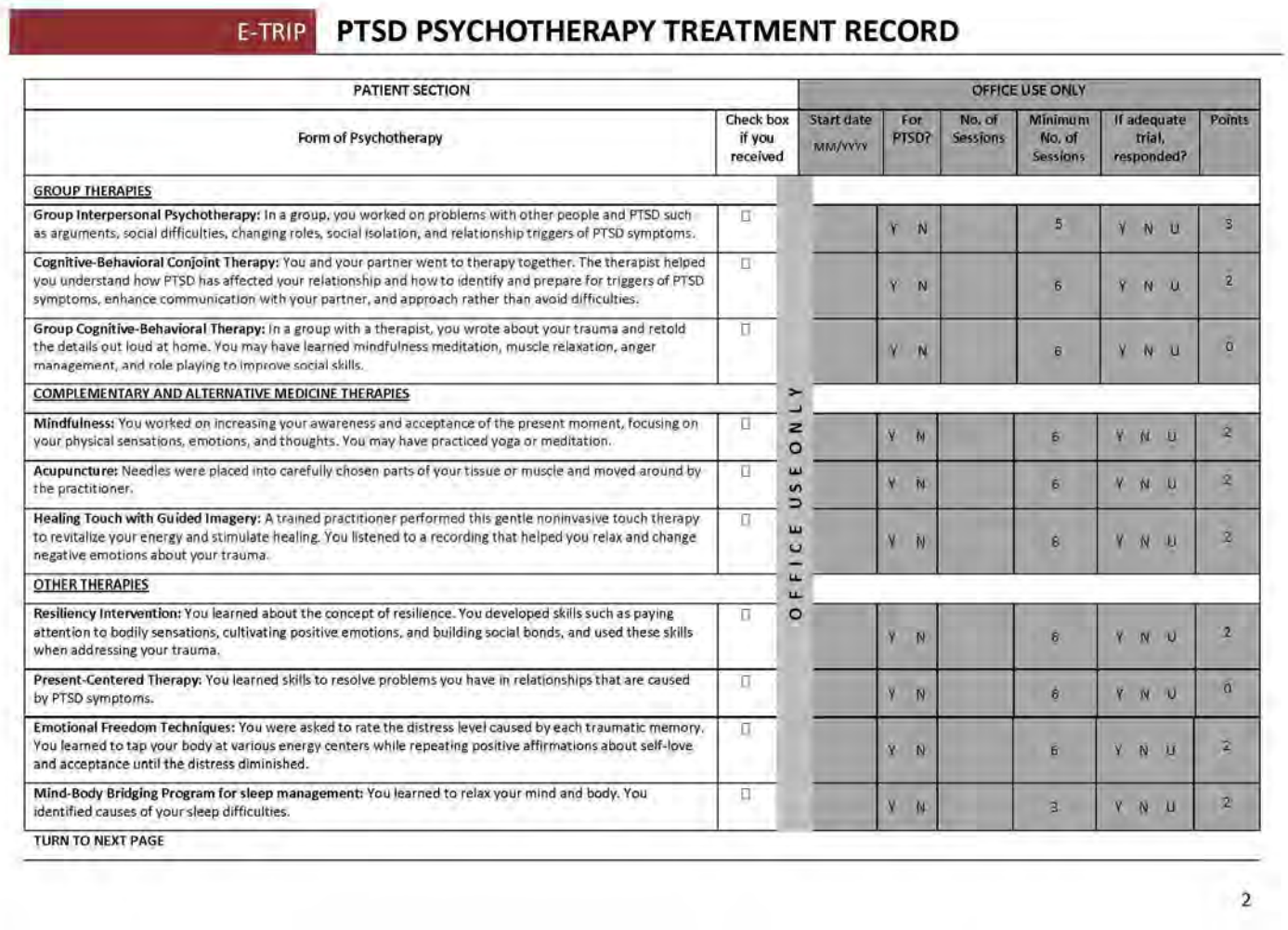

E-TRIP **PTSD PSYCHOTHERAPY TREATMENT RECORD**

PATIENT SECTION		OFFICE USE ONLY					
Form of Psychotherapy	Check box if you received	Start date MM/YYYY	For PTSD?	No. of Sessions	Minimum No. of Sessions	If adequate trial, responded?	Points
GROUP THERAPIES							
Group Interpersonal Psychotherapy: In a group, you worked on problems with other people and PTSD such as arguments, social difficulties, changing roles, social isolation, and relationship triggers of PTSD symptoms.	☐		Y N		5	Y N U	3
Cognitive-Behavioral Conjoint Therapy: You and your partner went to therapy together. The therapist helped you understand how PTSD has affected your relationship and how to identify and prepare for triggers of PTSD symptoms, enhance communication with your partner, and approach rather than avoid difficulties.	☐		Y N		6	Y N U	2
Group Cognitive-Behavioral Therapy: In a group with a therapist, you wrote about your trauma and retold the details out loud at home. You may have learned mindfulness meditation, muscle relaxation, anger management, and role playing to improve social skills.	☐		Y N		6	Y N U	0
COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES							
Mindfulness: You worked on increasing your awareness and acceptance of the present moment, focusing on your physical sensations, emotions, and thoughts. You may have practiced yoga or meditation.	☐		Y N		6	Y N U	2
Acupuncture: Needles were placed into carefully chosen parts of your tissue or muscle and moved around by the practitioner.	☐		Y N		6	Y N U	2
Healing Touch with Guided Imagery: A trained practitioner performed this gentle noninvasive touch therapy to revitalize your energy and stimulate healing. You listened to a recording that helped you relax and change negative emotions about your trauma.	☐		Y N		6	Y N U	2
OTHER THERAPIES							
Resiliency Intervention: You learned about the concept of resilience. You developed skills such as paying attention to bodily sensations, cultivating positive emotions, and building social bonds, and used these skills when addressing your trauma.	☐		Y N		6	Y N U	2
Present-Centered Therapy: You learned skills to resolve problems you have in relationships that are caused by PTSD symptoms.	☐		Y N		6	Y N U	0
Emotional Freedom Techniques: You were asked to rate the distress level caused by each traumatic memory. You learned to tap your body at various energy centers while repeating positive affirmations about self-love and acceptance until the distress diminished.	☐		Y N		6	Y N U	2
Mind-Body Bridging Program for sleep management: You learned to relax your mind and body. You identified causes of your sleep difficulties.	☐		Y N		3	Y N U	2

OFFICE USE ONLY

TURN TO NEXT PAGE

2

E-TRIP PTSD PSYCHOTHERAPY TREATMENT RECORD

PATIENT SECTION		OFFICE USE ONLY					
Form of Psychotherapy	Check box if you received	Start date MM/YYYY	For PTSD?	No. of Sessions	Minimum No. of Sessions	If adequate trial, responded?	Points
Supportive Therapy (ex. Rogerian Therapy, Talk Therapy): You talked with your therapist about what was going on in your life and the kinds of stresses you were facing. The therapist encouraged and supported you and gave advice about how to manage problems.	☐		Y N		6	Y N U	0
Relaxation: You learned and practiced techniques to relax. These may include focusing on your breath, muscle relaxation, visualization, or the repetition of positive messages.	☐		Y N		6	Y N U	0
COMBINATION THERAPIES							
Acupoint Stimulation added to Cognitive-Behavioral Therapy: A needle was placed in a specific part of your body. A small electrical charge was sent through the needle.	☐		Y N		5	Y N U	1
Skills Training in Affective and Interpersonal Regulation (STAIR): You worked on social skills like being more aware, flexible and assertive. You learned techniques to regulate your emotions. You described your trauma in detail.	☐		Y N		6	Y N U	0
Medication: You were given one of the following medications just before or after the therapy session to make the therapy work better. Choose from list below.	☐		Y N		n/a	Y N U	0
• **D-Cycloserine (DCS)**	☐		Y N		n/a	Y N U	0
• **Methylene Blue**	☐		Y N		n/a	Y N U	0
• **Oxytocin**	☐		Y N		n/a	Y N U	0
• **Yohimbine**	☐		Y N		n/a	Y N U	0
• **Dexamethasone/Hydrocortisone/Prednisone**	☐		Y N		n/a	Y N U	0
• **MDMA ("Ecstasy")**	☐		Y N		n/a	Y N U	0
• **Propranolol (Inderal)**	☐		Y N		n/a	Y N U	0

OFFICE USE ONLY

PSYCHOTHERAPY TOTAL POINTS: _____

3

E-TRIP **(EMORY TREATMENT RESISTANCE INTERVIEW FOR PTSD)**

PATIENT: **DATE:** **INTERVIEWER:**

Hand the E-TRIP PTSD Medication Treatment Record and E-TRIP PTSD Psychotherapy Treatment Record to the patient.

INTERVIEW

1. Clarify date of onset of PTSD.
   ASK: ***When did your symptoms of PTSD begin?***
   Provide the patient with examples of PTSD symptoms if they are unsure.

2. Determine primary PTSD symptoms and impairments in functioning that led patient to seek treatment.
   ASK: ***What kinds of PTSD symptoms were you experiencing that caused you to seek treatment?***
   IF PATIENT IS UNCERTAIN, ASK: ***For example, did you have intrusive memories of the trauma, nightmares, or flashbacks?***
   - ***Did you make excessive efforts to avoid thinking about the event or avoid reminders of it?***
   - ***Did you feel distant from other people or lose interest in activities you once enjoyed?***
   - ***Did you have problems with sleep, concentration, or irritability?***

PROCEED THROUGH NUMBERS 3-5 FOR EACH MEDICATION TAKEN, ONE AT A TIME.
PROCEED THROUGH NUMBERS 6-8 FOR EACH PSYCHOTHERAPY RECEIVED, ONE AT A TIME.

PTSD MEDICATION TREATMENT RECORD

On the PTSD Medication Treatment Record, if the patient checked "No," skip to Page 3 to assess psychotherapy treatments. If the patient checked "Yes," continue below.

3. Confirm that the medication checked was taken after the date of onset of PTSD.

Start Date MM/YYYY — ASK: ***When did you start taking the*** *(MEDICATION NAME)**?*** Record in the E-TRIP PTSD Medication Treatment Record.

For PTSD? — If the medication trial began **before** the onset of PTSD symptoms, circle "N" and **do not continue** to ask about the specific medication; if the medication trial began **after** the onset of PTSD symptoms, circle "Y" and **continue** to ask about the medication.

1

E-TRIP (EMORY TREATMENT RESISTANCE INTERVIEW FOR PTSD)

4. Determine if the medication treatment constituted an adequate trial. For each medicine taken for PTSD:

a. Dose used ASK: ***What was the highest dose of the*** *(MEDICATION NAME)* ***you took?*** Record in the E-TRIP PTSD Medication Treatment Record.

Minimum effective dose	If the dose reported is **less** than the minimally effective dose for that medication, **do not continue** to assess the specific medication. If it is **greater than or equal to** the minimally effective dose, **continue** to assess the medication.

b. Determine if the medication was used as monotherapy or as an augmentation ("add on") agent.

ASK: ***Was this medicine added on to a medicine you were already taking, so that you were taking both medicines on the same days?*** (If yes) ***Which medicine was it added on to?*** Record here. _____

Used to augment?	• If the patient did not take the medication to augment another medication, circle "N." • If the patient did take the medication to augment another medication, look up the point value for the medication you recorded in the above blank. ○ If the point value is **0 or 1 points or not listed,** do not continue to assess the augmentation medication; circle "N." ○ If the point value is **2 or 3 points**, the add-on medication is considered an augmentation agent, so circle "Y" under the Augment column and continue.

c. Determine the number of weeks that the patient took the medication.

≥8 weeks? ASK: ***For how many weeks in a row did you take that dose of*** *(MEDICATION NAME)****?*** Record in the E-TRIP PTSD Medication Treatment Record.

If the patient took dose for **<8 weeks,** circle N and **do not continue**. If the patient took dose for **≥ 8 weeks,** circle Y and **continue.**

NOTE: When eszopiclone is used for augmentation, ≥3 weeks constitutes an adequate trial; 8 weeks is not required.

d. Determine how many days the patient took the medication each week.

≥6 days/week? ASK: ***When you were taking that dose, did you take your*** *(MEDICATION NAME)* ***at least 6 days per week?***

Record in table: if the patient **did not** take the medication for at least 6 days per week, circle "N" and **do not continue** to assess this medication. If the patient **did** take the medication for at least 6 days per week, circle "Y" and **continue. This is an adequate trial.**

Patient responses should be confirmed using pharmacy prescription records or physicians' notes whenever such records are available.

2

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E-TRIP (EMORY TREATMENT RESISTANCE INTERVIEW FOR PTSD)

5. **Responded? (Y, N, U)** Determine if the patient responded to each treatment. Response to a treatment is defined as ≥30% improvement in PTSD symptomatology.

a. Assess Symptom Improvement. ASK: ***Which symptoms that you listed in the beginning of the interview*** (refer to patient's presenting problems on page 1, question 2) ***improved or did not improve?***

IF STILL UNSURE IF SYMPTOMS IMPROVED, ASK QUESTIONS BELOW:

- ***What did your family members or friends say about your response to the treatment?***
- ***Did you feel*** *(MEDICATION NAME)* ***made a clear difference in how you felt? Can you give me some examples of how it helped you?***

ASK: ***Considering all of these symptoms together, what percentage do you think your PTSD symptoms improved on this medication?***

RECORD:
- ☐ 0-29% improvement: non-response (N)
- ☐ 30-100% improvement: response (Y)
- ☐ Unsure of improvement (U)

NOTE: Patients who initially responded to a treatment, then lost response to the same treatment at a later time and never regained response should be scored as having a non-response to that treatment.

Points Code response on the E-TRIP PTSD medication treatment record. If the patient's PTSD symptoms improved 0-29% while taking the medication, circle "N." If the patient's PTSD symptoms improved 30-100% while taking the medication, circle "Y." If it is unclear if the patient's PTSD symptoms improved, circle "U." If you circled **"N," go to the "Points" column for that medication and circle the number listed.**

NOTE: A maximum of **TWO** failed SSRI treatment trials should be scored, so that the maximum number of points for failing to respond to SSRI medications is 6. Additional failed trials of SSRIs should not be scored.

REPEAT QUESTIONS 3-5 FOR EACH MEDICATION TAKEN.

After assessing all medication trials, add **total points** for nonresponse to adequate trials of medication treatments and **record** at the bottom of the E-TRIP PTSD Medication Treatment Record.

PTSD PSYCHOTHERAPY TREATMENT RECORD

On the E-TRIP PTSD Psychotherapy Treatment Record, if the patient checked "No," end the interview. If the patient checked "Yes," continue.

6. Confirm that the psychotherapy checked was started after the date of onset of PTSD.

Start Date MM/YYYY ASK: ***When did you begin treatment with*** *(PSYCHOTHERAPY NAME)****?*** Record in table.

For PTSD? If the psychotherapy began **before** the onset of PTSD symptoms, circle "N" and **do not continue** to ask about the specific psychotherapy; if the psychotherapy began **after** the onset of PTSD symptoms, circle "Y" and **continue** to ask about the psychotherapy.

If the patient checked multiple psychotherapies that occurred in a similar time frame, determine whether the separate therapies were actually conducted as part of a more comprehensive treatment package (e.g. "Relaxation" performed as part of prolonged exposure).

3

E-TRIP (EMORY TREATMENT RESISTANCE INTERVIEW FOR PTSD)

7. Determine if each treatment constituted an adequate trial.

ASK: ***How many sessions of*** *(PSYCHOTHERAPY NAME)* ***did you receive?*** Record in the E-TRIP PTSD Psychotherapy Treatment Record.

Minimum No. of Sessions	If the patient received **less** than the minimum number of sessions for that psychotherapy, **do not continue** to ask about the psychotherapy. If the patient received **greater than or equal** the minimum number of sessions, **continue** to ask about the psychotherapy. **This is an adequate trial.**

8. Responded? (Y, N, U) Determine if the patient responded to each treatment. Response to a treatment is defined as ≥30% improvement in PTSD symptomatology.

a. Assess Symptom Improvement. (ASK) ***Which symptoms that you listed in the beginning of the interview*** (refer to patient's presenting problems on page 1, question 2) ***improved or did not improve?***

IF STILL UNSURE IF SYMPTOMS IMPROVED, ASK QUESTIONS BELOW:

- ***What did your family members or friends say about your response to the treatment?***
- ***Did you feel*** *(PSYCHOTHERAPY NAME)* ***made a clear difference in how you felt? Can you give me some examples of how it helped you?***

ASK: ***Considering all of these symptoms together, what percentage do you think your PTSD symptoms improved over the course of this psychotherapy?***

RECORD:
- ☐ 0-29% improvement: non-response (N)
- ☐ 30-100% improvement: response (Y)
- ☐ Unsure of improvement (U)

NOTE: Patients who initially responded to a treatment, then lost response to the same treatment at a later time and never regained response should be scored as having a non-response to that treatment.

Points Code response on the E-TRIP PTSD Psychotherapy Treatment Record. If the patient's PTSD symptoms improved 0-29% over the course of the psychotherapy, circle "N." If the patient's PTSD symptoms improved 30-100% over the course of the psychotherapy, circle "Y." If it is unclear if the patient's PTSD symptoms improved, circle "U." If you circled **"N," go to the "Points" column for that medication and circle the number listed.**

REPEAT QUESTIONS 6-8 FOR EACH PSYCHOTHERAPY RECEIVED.
After assessing all psychotherapy trials, add **total points** for nonresponse to adequate trials of psychotherapy treatments and **record** at the bottom of the E-TRIP Psychotherapy Treatment Record.

POINTS: **MEDICATION** _____
PSYCHOTHERAPY _____
TOTAL _____

4

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Appendix 12 Life Events Checklist for DSM-5 (LEC-5)

LEC-5

Part 1

Instructions: Listed below are a number of difficult or stressful things that sometimes happen to people. For each event check one or more of the boxes to the right to indicate that: (a) it happened to you personally; (b) you witnessed it happen to someone else; (c) you learned about it happening to a close family member or close friend; (d) you were exposed to it as part of your job (for example, paramedic, police, military, or other first responder); (e) you're not sure if it fits; or (f) it doesn't apply to you.

Be sure to consider your *entire life* (growing up as well as adulthood) as you go through the list of events.

Event	Happened to me	Witnessed it	Learned about it	Part of my job	Not sure	Doesn't apply
1. Natural disaster (for example, flood, hurricane, tornado, earthquake)						
2. Fire or explosion						
3. Transportation accident (for example, car accident, boat accident, train wreck, plane crash)						
4. Serious accident at work, home, or during recreational activity						
5. Exposure to toxic substance (for example, dangerous chemicals, radiation)						
6. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up)						
7. Assault with a weapon (for example, being shot, stabbed, threatened with a knife, gun, bomb)						
8. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)						
9. Other unwanted or uncomfortable sexual experience						
10. Combat or exposure to a war-zone (in the military or as a civilian)						
11. Captivity (for example, being kidnapped, abducted, held hostage, prisoner of war)						
12. Life-threatening illness or injury						
13. Severe human suffering						
14. Sudden violent death (for example, homicide, suicide)						
15. Sudden accidental death						
16. Serious injury, harm, or death you caused to someone else						
17. Any other very stressful event or experience						

PLEASE COMPLETE PART 2 ON THE FOLLOWING PAGE

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Part 2:

A. If you checked anything for #17 in PART 1, briefly identify the event you were thinking of:

_____

_____

B. If you have experienced more than one of the events in PART 1, think about the event you consider the worst event, which for this questionnaire means the event that currently bothers you the most. If you have experienced only one of the events in PART 1, use that one as the worst event. Please answer the following questions about the worst event (check all options that apply):

1. Briefly describe the worst event (for example, what happened, who was involved, etc.).

   _____

   _____

2. How long ago did it happen? _____ (please estimate if you are not sure)

3. How did you experience it?
   - ____ It happened to me directly
   - ____ I witnessed it
   - ____ I learned about it happening to a close family member or close friend
   - ____ I was repeatedly exposed to details about it as part of my job (for example, paramedic, police, military, or other first responder)
   - ____ Other, please describe: _____

4. Was someone's life in danger?
   - ____ Yes, my life
   - ____ Yes, someone else's life
   - ____ No

5. Was someone seriously injured or killed?
   - ____ Yes, I was seriously injured
   - ____ Yes, someone else was seriously injured or killed
   - ____ No

6. Did it involve sexual violence? ____Yes ____No

7. If the event involved the death of a close family member or close friend, was it due to some kind of accident or violence, or was it due to natural causes?
   - ____ Accident or violence
   - ____ Natural causes
   - ____ Not applicable (The event did not involve the death of a close family member or close friend)

8. How many times altogether have you experienced a similar event as stressful or nearly as stressful as the worst event?
   - ____ Just once
   - ____ More than once (please specify or estimate the total # of times you have had this experience _____)

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Appendix 13 Mini International Neuropsychiatric Interview (MINI)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

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.

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

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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	ICD-10-CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐		
		Past	☐		
		Recurrent	☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	☐	F32.x	☐
		Past	☐	F32.x	☐
		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	☐	F31.0 - F31.76	☐
		Past	☐	F31.0 - F31.76	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31.2/31.5/F31.64	☐
		Past	☐	F31.2/31.5/F31.64	☐
	BIPOLAR II DISORDER	Current	☐	F31.81	☐
		Past	☐	F31.81	☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current	☐	F31.89	☐
		Past	☐	F31.89	☐
D	PANIC DISORDER	Current (Past Month)	☐	F41.0	☐
		Lifetime	☐	F40.0	☐
E	AGORAPHOBIA	Current	☐	F40.00	☐
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	☐	F40.10	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42.2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43.10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10.10/F10.20	☐
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	☐	F11.10/F11.20 - F19.20	☐

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K	ANY PSYCHOTIC DISORDER	Current Lifetime	☐ ☐	F20.03-F29 F20.81-F29	☐ ☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past	☐ ☐	F32.3/F33.3 F32.3/F33.3	☐ ☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past	☐ ☐	F31.2/F31.5/F31.64 F31.2/F31.5/F31.64	☐ ☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50.01/F50.02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50.2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50.81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	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?)

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16) 3

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major 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:
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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?	NO	YES
		IF NO, CODE NO TO **A1b**. IF **YES** ASK:		
	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?	NO	YES
		IF NO, CODE NO TO **A2b**. IF **YES** ASK:		
	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?	NO	YES	NO	YES
	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				
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

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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.

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B. SUICIDALITY

				Points
	In the past month did you:			
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? IF NO TO **B1a**, SKIP TO **B2**. IF YES, ASK **B1b**:	NO	YES	0
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)? IF NO TO **B2 + B3**, SKIP TO **B4**. OTHERWISE ASK:	NO	YES	6

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, mark 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? IN ASSESSING WHETHER THIS WAS LARGELY UNPROVOKED ASK: "5 minutes before this impulse, could you have predicted it would occur at that time?" IF NO TO **B12**, SKIP TO **B14**.	NO	YES	8

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B13	Have difficulty resisting these impulses?	NO	YES	6
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 TO **B16c**, 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

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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 was 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	☐
In early remission	☐
In remission	☐

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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

d **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. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes	NO	YES	NO	YES
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

		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: 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 **3** OF THE **C3** SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **C3** SYMPTOMS.	NO	YES	NO	YES
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 consecutive days or less		☐		☐
	b) 4, 5 or 6 consecutive days or more		☐		☐
	c) 7 consecutive days or more		☐		☐
C5	Were you hospitalized for these problems? IF **YES**, CIRCLE **YES** IN MANIC EPISODE FOR THAT TIME FRAME AND GO TO **C7**.	NO	YES	NO	YES
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	☐

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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

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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		AM 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

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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 OF THE ABOVE SITUATIONS IN **E1** 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	

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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 CLINICIAN: 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 ☐

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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 **G3a**
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 **G3a**
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 (**G1a** AND **G1b** AND **G2**) OR (**G3a** AND **G3b**) 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 OBSESSIVE COMPULSIVE 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 ☐

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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

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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
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 ☐

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I. ALCOHOL USE DISORDER

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

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

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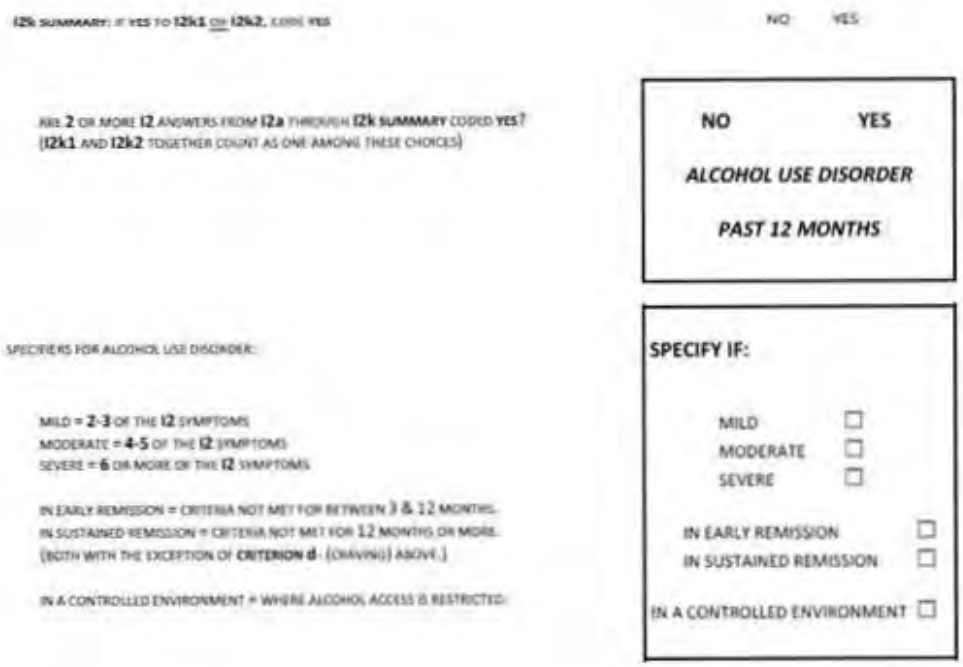

J. SUBSTANCE USE DISORDER (NON-ALCOHOL)

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

			➡ NO	YES
		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?		

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".

Sedatives, Hypnotics or Anxiolytics: Quaalude, Sesonal ("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

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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 APPROPRIATE 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 APPROPRIATE MEDICAL SUPERVISION.

Sedatives, Hypnotics or Anxiolytics (2 or more withdrawal symptoms)
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 withdrawal symptoms)
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 and Cocaine (2 or more withdrawal symptoms)
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 withdrawal symptoms)
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. ☐

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

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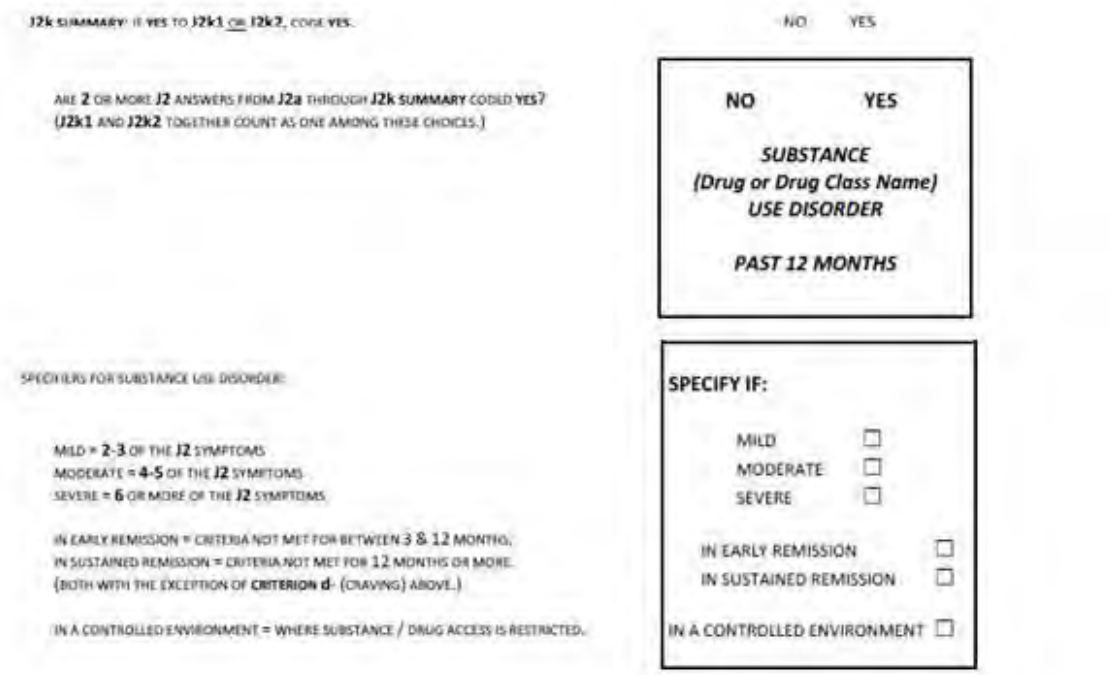

J2k SUMMARY: IF YES TO J2k1 OR J2k2, CODE YES.

NO YES

ARE 2 OR MORE J2 ANSWERS FROM J2a THROUGH J2k SUMMARY CODED YES?
(J2k1 AND J2k2 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 ☐

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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? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES
	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? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES
	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? CLINICIAN: 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.	NO	YES
	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

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K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES
	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**? **AND IS EITHER:** MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST) **OR** MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? **AND** HOW LONG HAS THE MOOD EPISODE LASTED? _____ HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? _____ IF SUCH A MOOD EPISODE IS PRESENT, CODE **YES** TO **K11a** ONLY IF THE MOOD DISTURBANCE IS PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE **NO**.	NO → **K13**	YES
		IF **NO** TO **K11a** AND THE TOTAL DURATION OF THE MOOD EPISODE IS **LESS THAN** THE TOTAL DURATION OF THE PSYCHOTIC EPISODE, THEN CIRCLE **NO** IN BOTH "MOOD DISORDER WITH PSYCHOTIC FEATURES" DIAGNOSTIC BOXES AND MOVE TO **K13**.		

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 **K1a** TO **K7a**) 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 EXPERIENCE (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

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 **2** 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

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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/M²

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/m² 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.

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M. BULIMIA NERVOSA

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN THE 3 BULIMIA SECTION DIAGNOSTIC BOXES, AND MOVE TO BINGE EATING DISORDER)

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
M2	During these binges, did you feel that your eating was out of control?	➡ NO	YES
M3	In the last 3 months, did you have eating binges as often as once a week?	➡ NO	YES
M4	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?	➡ NO	YES
M4a	Number of Episodes of Inappropriate Compensatory Behaviors per Week? _____ Number of Days of Inappropriate Compensatory Behaviors per Week? _____		
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 ↓ Skip to M8	YES
M7	Do these binges occur only when you are under (_____lb/kg)? CLINICIAN: 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**	

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

AND

IS **M2** OR **M4** 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	IS **M2** CODED **YES**?	➡ NO	YES
MB4	IS **M3** CODED **YES**?	➡ NO	YES
MB5	IS **M4** 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

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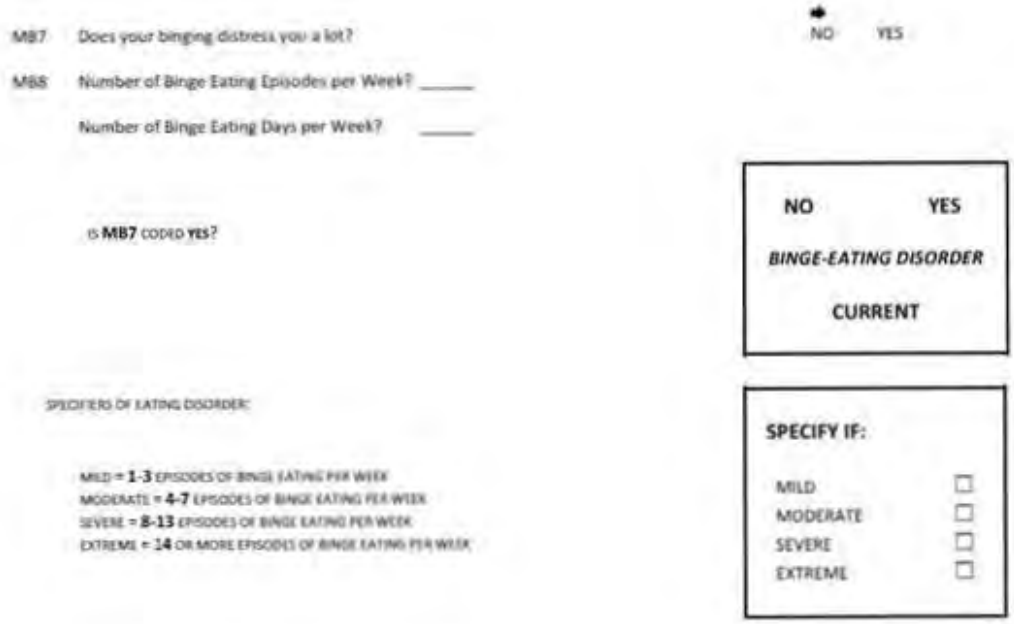

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N. GENERALIZED ANXIETY DISORDER

(➡ 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 OR A MAJOR DEPRESSIVE EPISODE OR A MANIC OR A HYPOMANIC EPISODE 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: HAS 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**. OTHERWISE IT IS UNCERTAIN.		☐ No	☐ Yes ☐ Uncertain

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P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS: SKIP ALL THE P2 QUESTIONS, 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

ADDITIONAL OPTIONAL INTERVIEW ASSESSMENTS ON PAGES 36 & 37

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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 IN ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7**	YES	YES
b	CIRCLE **YES** IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a** OR IN 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	☐

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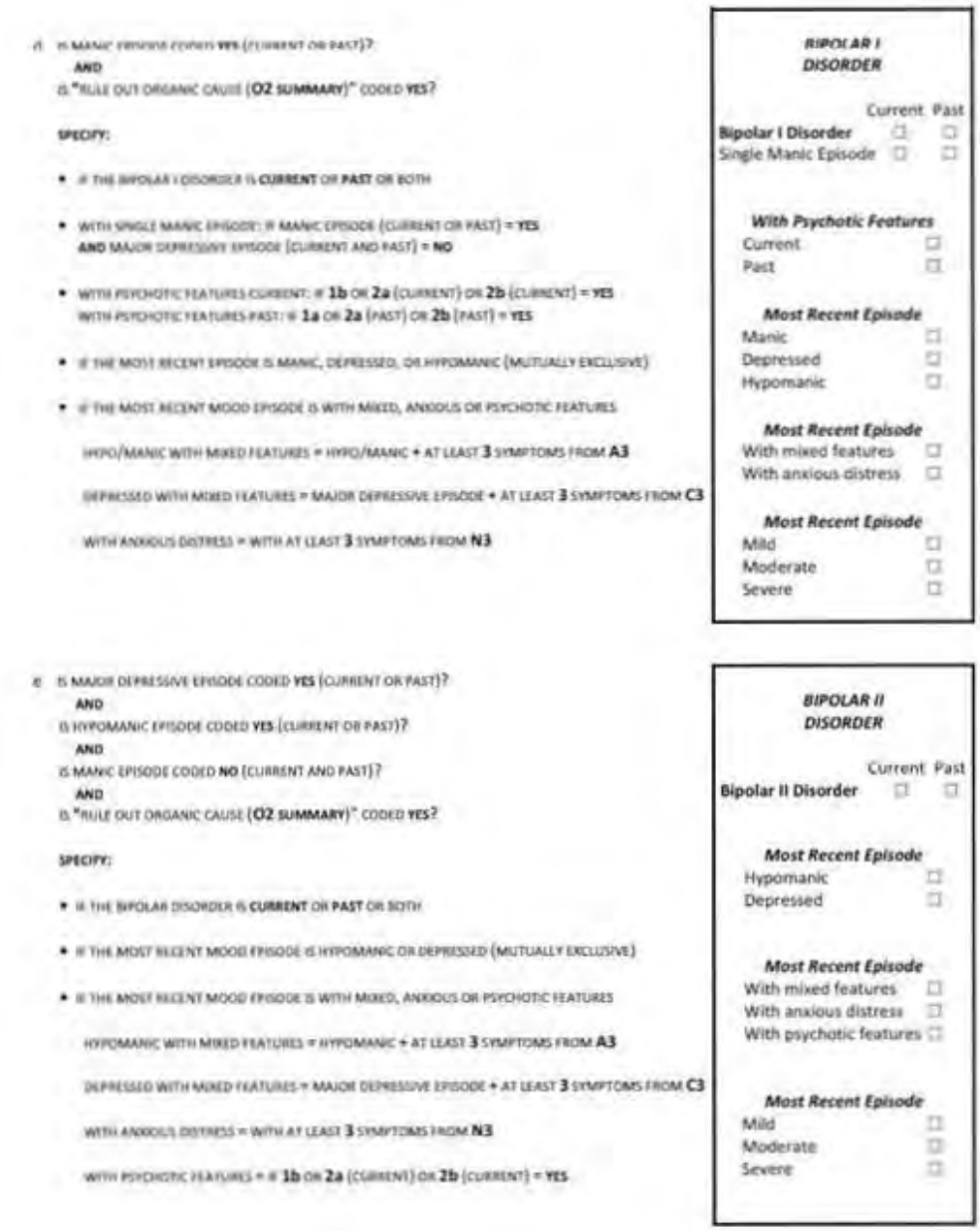

d. Is MANIC EPISODE CODED **YES** (CURRENT OR PAST)?
AND
Is "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- If THE BIPOLAR I DISORDER IS **CURRENT** OR **PAST** OR BOTH
- WITH SINGLE MANIC EPISODE: If MANIC EPISODE (CURRENT OR PAST) = **YES** **AND** MAJOR DEPRESSIVE EPISODE (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 (MUTUALLY EXCLUSIVE)
- If THE MOST RECENT MOOD EPISODE IS WITH MIXED, ANXIOUS OR PSYCHOTIC FEATURES
  HYPO/MANIC WITH MIXED FEATURES = HYPO/MANIC + AT LEAST **3** SYMPTOMS FROM **A3**
  DEPRESSED WITH MIXED FEATURES = MAJOR DEPRESSIVE EPISODE + AT LEAST **3** SYMPTOMS FROM **C3**
  WITH ANXIOUS DISTRESS = WITH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR I DISORDER

	Current	Past
Bipolar I Disorder	☐	☐
Single Manic Episode	☐	☐

With Psychotic Features
Current ☐
Past ☐

Most Recent Episode
Manic ☐
Depressed ☐
Hypomanic ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

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

SPECIFY:

- If THE BIPOLAR DISORDER IS **CURRENT** OR **PAST** OR BOTH
- If THE MOST RECENT MOOD EPISODE IS HYPOMANIC OR DEPRESSED (MUTUALLY EXCLUSIVE)
- If THE MOST RECENT MOOD EPISODE IS WITH MIXED, ANXIOUS OR PSYCHOTIC FEATURES
  HYPOMANIC WITH MIXED FEATURES = HYPOMANIC + AT LEAST **3** SYMPTOMS FROM **A3**
  DEPRESSED WITH MIXED FEATURES = MAJOR DEPRESSIVE EPISODE + AT LEAST **3** SYMPTOMS FROM **C3**
  WITH ANXIOUS DISTRESS = WITH AT LEAST **3** SYMPTOMS FROM **N3**
  WITH PSYCHOTIC FEATURES = If **1b** OR **2a** (CURRENT) OR **2b** (CURRENT) = **YES**

BIPOLAR II DISORDER

	Current	Past
Bipolar II Disorder	☐	☐

Most Recent Episode
Hypomanic ☐
Depressed ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐
With psychotic features ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

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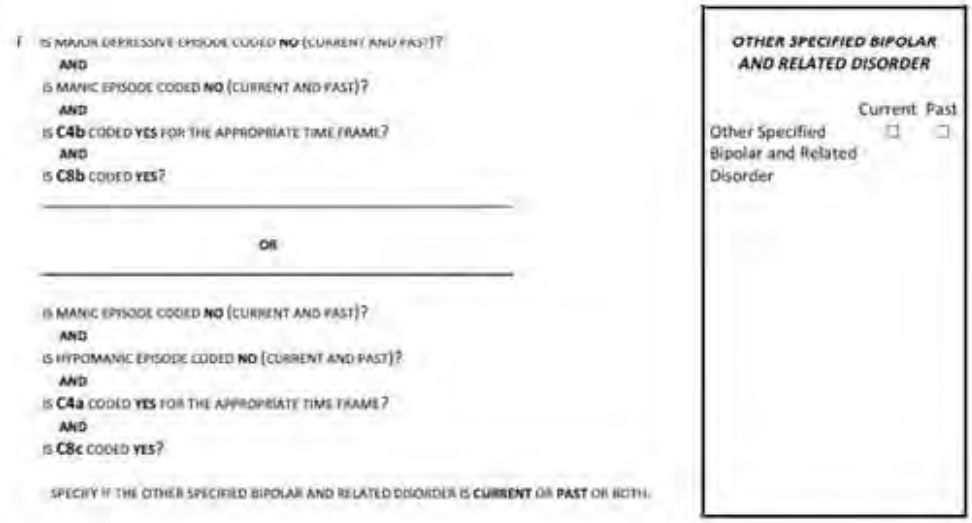

IF IS MAJOR DEPRESSIVE EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS **C4b** CODED **YES** FOR THE APPROPRIATE TIME FRAME?
AND
IS **C8b** CODED **YES**?

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 OTHER SPECIFIED BIPOLAR AND RELATED DISORDER IS **CURRENT** OR **PAST** OR BOTH.

OTHER SPECIFIED BIPOLAR AND RELATED DISORDER

	Current	Past
Other Specified Bipolar and Related Disorder	☐	☐

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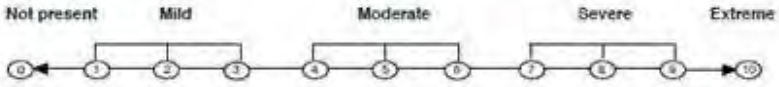
OPTIONAL ASSESSMENT MEASURES TO TRACK CHANGES OVER TIME

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, impulses, plans, intent, (ANY thoughts of killing yourself), or any preparations to kill yourself or ANY attempt to kill 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 or obsessive thoughts or compulsive 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	
13	Overusing alcohol or drugs	

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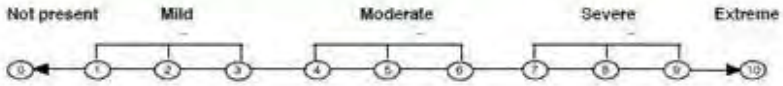
B: DISABILITY / FUNCTIONAL IMPAIRMENT

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?	

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   A. Carlo Altamura, Milano, Italy
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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
	MDD WITH ANXIOUS DISTRESS	Current (2 weeks)
	MDD WITH MIXED FEATURES	Current (2 weeks)
	MDD WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDD WITH ATYPICAL FEATURES	Current (2 weeks)
	MDD WITH PSYCHOTIC FEATURES	Current (2 weeks)
	MDD WITH CATATONIA	Current (2 weeks)
	MDD WITH SEASONAL PATTERN	Current (2 weeks)
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past
	SUBSTANCE- / MEDICATION-INDUCED DEPRESSIVE DISORDER	Current (2 weeks) Past
	DEPRESSIVE DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current (2 weeks) Past
AY	PERSISITENT DEPRESSIVE DISORDER	Current
	OTHER SPECIFIED DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent
B	SUICIDALITY	Current (Past Month) ☐ Lifetime attempt ☐ ☐Low ☐Moderate ☐High
	SUICIDE BEHAVIOR DISORDER	Current ☐ (In Past Year) In early remission ☐ (1 - 2 Years Ago) In remission ☐ (> 2 Years Ago)
C	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past
	SUBSTANCE- / MEDICATION-INDUCED BIPOLAR DISORDER AND RELATED DISORDER	Current (2 weeks) Past

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	BIPOLAR DISORDER AND RELATED DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	OTHER SPECIFIED BIPOLAR DISORDER AND RELATED DISORDER	Current (2 weeks) Past
	UNSPECIFIED BIPOLAR AND RELATED DISORDER	Current (2 weeks) Past
D	PANIC DISORDER	Current (Past Month) Lifetime
E	AGORAPHOBIA	Current
F	SOCIAL ANXIETY DISORDER (Social Phobia) Performance only type ☐	Current (Past Month)
FA	SPECIFIC PHOBIA	Current
	SUBSTANCE- / MEDICATION-INDUCED ANXIETY DISORDER	Current
	ANXIETY DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current
G	OBSESSIVE-COMPULSIVE DISORDER (OCD)	Current (Past Month)
	SUBSTANCE- / MEDICATION-INDUCED OBSESSIVE- COMPULSIVE DISORDER AND RELATED DISORDER	Current (2 weeks) Past
	OBSESSIVE-COMPULSIVE AND RELATED DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	HOARDING DISORDER	Current
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
HL	POSTTRAUMATIC STRESS DISORDER	Lifetime
HAS	ACUTE STRESS DISORDER	Current (2 weeks)
I	ALCOHOL USE DISORDER	Past 12 Months
IL	ALCOHOL USE DISORDER	Lifetime
J	SUBSTANCE USE DISORDER	Past 12 Months
JL	SUBSTANCE USE DISORDER (Non-alcohol)	Lifetime
K	ANY PSYCHOTIC DISORDER	Current Lifetime
	SCHIZOPHRENIA	Current Lifetime
	SCHIZOAFFECTIVE DISORDER Bipolar type ☐ Depressive type ☐	Current Lifetime
	SCHIZOPHRENIFORM DISORDER	Current Lifetime
	BRIEF PSYCHOTIC DISORDER	Current Lifetime
	DELUSIONAL DISORDER	Current Lifetime
	SUBSTANCE- / MEDICATION-INDUCED PSYCHOTIC DISORDER	Current Lifetime
	PSYCHOTIC DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current Lifetime

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	OTHER SPECIFIED SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER	Current Lifetime
	UNSPECIFIED SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER	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)
MB	BINGE-EATING DISORDER	Current (Past 3 Months)
N	GENERALIZED ANXIETY DISORDER (GAD)	Current (Past 6 Months)
	SUBSTANCE- / MEDICATION-INDUCED GAD	Current
	GAD DUE TO ANOTHER MEDICAL CONDITION	Current
O	SOMATIC SYMPTOM DISORDER	Current
P	ILLNESS ANXIETY DISORDER	Current
Q	BODY DYSMORPHIC DISORDER	Current
R	INTERMITTENT EXPLOSIVE DISORDER	Current
S	CONDUCT DISORDER	Current (past 12 months)
T	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Children /Adolescents)
	ADHD COMBINED PRESENTATION ☐	
	ADHD PREDOMINANTLY INATTENTIVE PRESENTATION ☐	
	ADHD PREDOMINANTLY HYPERACTIVE / IMPULSIVE PRESENTATION ☐	
TA	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Adults)
	ADHD COMBINED PRESENTATION ☐	
	ADHD PREDOMINANTLY INATTENTIVE PRESENTATION ☐	
	ADHD PREDOMINANTLY HYPERACTIVE / IMPULSIVE PRESENTATION ☐	
U	PREMENSTRUAL DYSPHORIC DISORDER	Current
V	ADJUSTMENT DISORDERS	Current
W	BORDERLINE PERSONALITY DISORDER	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 and the standard MINI is sufficient.

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. For information on the availability and licensing of any version of the MINI, whether computerized or paper / pdf versions, contact David Sheehan MD MBA at davidvsheehan@gmail.com

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Appendix 14 Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)

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Name:_____ Current Age: _____ Interviewer Initials: _____ Date: _____

Ohio State University TBI Identification Method — Interview Form

Step 1

Ask questions 1-5 below. Record the cause of each reported injury and any details provided spontaneously in the chart at the bottom of this page. You do not need to ask further about loss of consciousness or other injury details during this step.

I am going to ask you about injuries to your head or neck that you may have had anytime in your life.

1. In your lifetime, have you ever been hospitalized or treated in an emergency room following an injury to your head or neck? Think about any childhood injuries you remember or were told about.
   ☐ No ☐ Yes—Record cause in chart
2. In your lifetime, have you ever injured your head or neck in a car accident or from crashing some other moving vehicle like a bicycle, motorcycle or ATV?
   ☐ No ☐ Yes—Record cause in chart
3. In your lifetime, have you ever injured your head or neck in a fall or from being hit by something (for example, falling from a bike or horse, rollerblading, falling on ice, being hit by a rock)? Have you ever injured your head or neck playing sports or on the playground?
   ☐ No ☐ Yes—Record cause in chart
4. In your lifetime, have you ever injured your head or neck in a fight, from being hit by someone, or from being shaken violently? Have you ever been shot in the head?
   ☐ No ☐ Yes—Record cause in chart
5. In your lifetime, have you ever been nearby when an explosion or a blast occurred? If you served in the military, think about any combat- or training-related incidents.
   ☐ No ☐ Yes—Record cause in chart

Interviewer instruction:
If the answers to any of the above questions are "yes," go to Step 2. If the answers to all of the above questions are "no," then proceed to Step 3.

Step 2

Interviewer instruction: If the answer is "yes" to any of the questions in Step 1 ask the following additional questions about each reported injury and add details to the chart below.

Were you knocked out or did you lose consciousness (LOC)?

If yes, how long?

If no, were you dazed or did you have a gap in your memory from the injury?

How old were you?

Step 3

Interviewer instruction: Ask the following questions to help identify a history that may include multiple mild TBIs and complete the chart below.

Have you ever had a period of time in which you experienced multiple, repeated impacts to your head (e.g. history of abuse, contact sports, military duty)?

If yes, what was the typical or usual effect—were you knocked out (Loss of Consciousness - LOC)?

If no, were you dazed or did you have a gap in your memory from the injury?

What was the most severe effect from one of the times you had an impact to the head?

How old were you when these repeated injuries began? Ended?

Step 1	Step 2						
	Loss of consciousness (LOC)/knocked out				Dazed/Mem Gap		Age
Cause:	No LOC	< 30 min	30 min-24 hrs	> 24 hrs	Yes	No	

If more injuries with LOC: How many?_____ Longest knocked out?_____ How many ≥ 30 mins?_____ Youngest age? _____

Step 3	Typical Effect		Most Severe Effect				Age	
Cause of repeated injury	Dazed/ memory gap, no LOC	LOC	Dazed/ memory gap, no LOC	LOC < 30 min	LOC 30 min - 24 hrs.	LOC > 24 hrs.	Began	Ended

Adapted with permission from the Ohio State University TBI Identification Method (Corrigan JD, Bogner JA, 2007). Initial reliability and validity of the OSU TBI Identification Method. J Head Trauma Rehabil. 22(6):318-329. © Research Foundation, The Ohio State University, 2005. All rights reserved.

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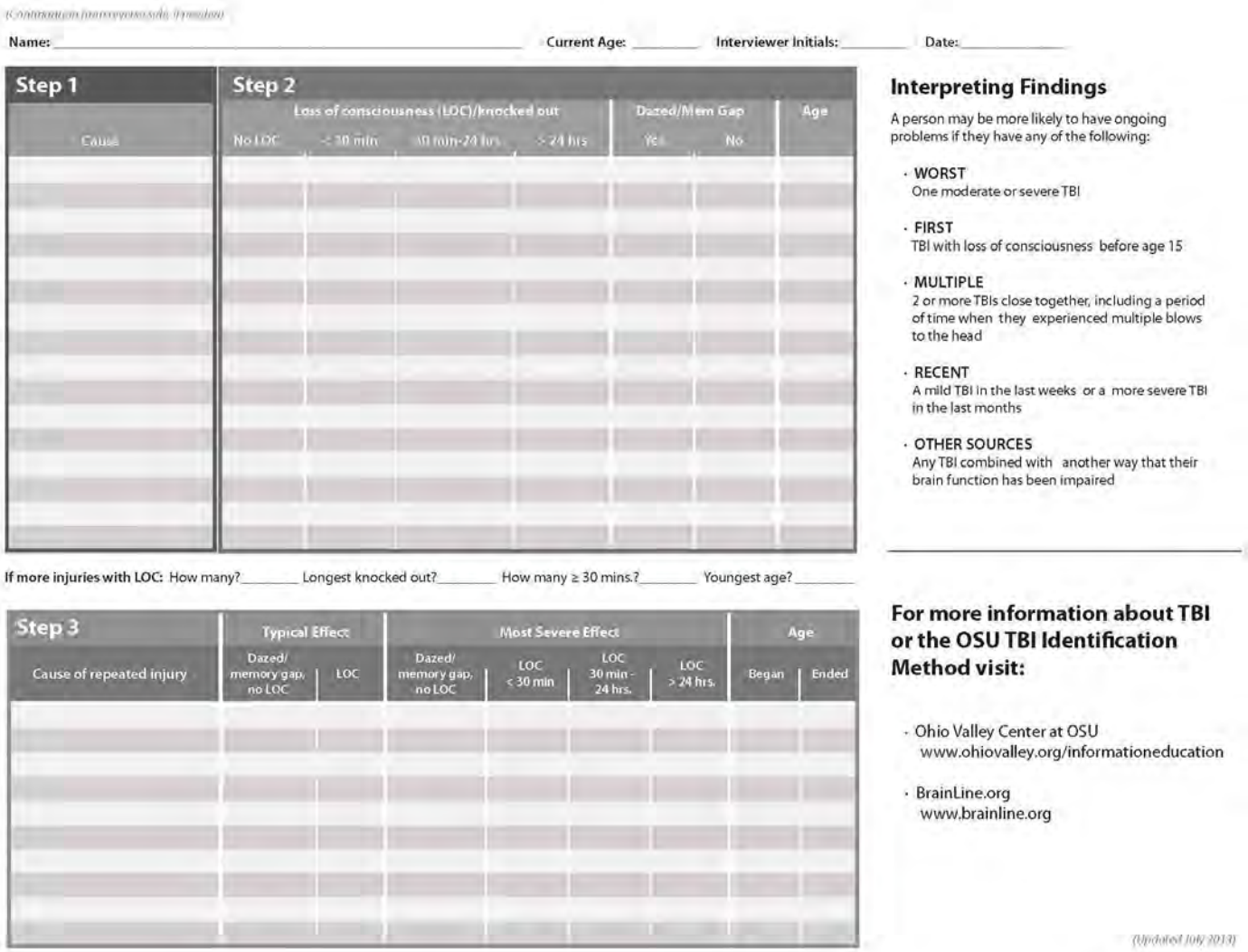

Name: _____ Current Age: _____ Interviewer Initials: _____ Date: _____

Step 1	Step 2						
	Loss of consciousness (LOC)/knocked out				Dazed/Mem Gap		Age
Cause	No LOC	< 30 min	30 min-24 hrs	> 24 hrs	Yes	No	

If more injuries with LOC: How many?_____ Longest knocked out?_____ How many ≥ 30 mins.?_____ Youngest age?_____

Step 3	Typical Effect		Most Severe Effect				Age	
Cause of repeated injury	Dazed/ memory gap, no LOC	LOC	Dazed/ memory gap, no LOC	LOC < 30 min	LOC 30 min - 24 hrs.	LOC > 24 hrs.	Began	Ended

Interpreting Findings

A person may be more likely to have ongoing problems if they have any of the following:

- **WORST**
  One moderate or severe TBI
- **FIRST**
  TBI with loss of consciousness before age 15
- **MULTIPLE**
  2 or more TBIs close together, including a period of time when they experienced multiple blows to the head
- **RECENT**
  A mild TBI in the last weeks or a more severe TBI in the last months
- **OTHER SOURCES**
  Any TBI combined with another way that their brain function has been impaired

For more information about TBI or the OSU TBI Identification Method visit:

- Ohio Valley Center at OSU
  www.ohiovalley.org/informationeducation
- BrainLine.org
  www.brainline.org

(Updated July 2013)

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Appendix 15 Abnormal Involuntary Movement Scale (AIMS)

Movement ratings: rate highest severity observed. Rate movements that occur upon activation one **less** than those observed spontaneously.		**Code for items 1-7:** **0** = None **1** = Minimal, may be extreme normal **2** = Mild **3** = Moderate **4** = Severe
		(Circle One)
FACIAL AND ORAL MOVEMENTS:	**1.** **MUSCLES OF FACIAL EXPRESSION** e.g. movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	**0 1 2 3 4**
	2. **LIPS AND PERIORAL AREA** e.g. puckering, pouting, smacking.	**0 1 2 3 4**
	3. **JAW** e.g. biting, clenching, chewing, mouth opening, lateral movement.	**0 1 2 3 4**
	4. **TONGUE** Rate only increase in movement both in and out of mouth, not inability to sustain movement.	**0 1 2 3 4**
EXTREMITY MOVEMENTS:	**5.** **UPPER (ARMS, WRISTS, HANDS, FINGERS)** include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e. slow, irregular, complex, serpentine). Do not include tremor (i.e. repetitive, regular, rhythmic).	**0 1 2 3 4**
	6. **LOWER (LEGS, KNEES, ANKLES, TOES)** e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	**0 1 2 3 4**
TRUNK MOVEMENTS:	**7.** **NECK, SHOULDERS, HIPS** e.g. rocking, twisting, squirming, pelvic gyrations	**0 1 2 3 4**
GLOBAL JUDGMENTS:	**8.** Severity of abnormal movements	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**
	9. Incapacitation due to abnormal movements	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**
	10. Patient's awareness of abnormal movements Rate only subject's report.	No awareness **0** Aware, no distress **1** Aware, mild distress **2** Aware, moderate distress **3** Aware, severe distress **4**
DENTAL STATUS:	**11.** Any current problems with teeth and/or dentures?	No **0** Yes **1**
	12. Does patient usually wear dentures?	No **0** Yes **1**

Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

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Appendix 16 Barnes Akathisia Rating Scale (BARS)

Instructions

Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of 2 minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, and/or complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time and/or reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

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Global clinical assessment of akathisia

0 *Absent*. No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 *Questionable*. Non-specific inner tension and fidgety movements

2 Mild akathisia. Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 *Moderate akathisia*. Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 *Marked akathisia*. Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing

5 *Severe akathisia*. The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

Reproduced from: A rating scale for drug-induced akathisia. T.R.E. Barnes, *British Journal of Psychiatry* (1989), **154**, 672-676.

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Appendix 17 Simpson-Angus Scale (SAS)

Circle the appropriate score for each item:	
1.	**GAIT** The patient is examined as he walks into the examining room; his gait, the swing of arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:
0	Normal
1	Mild diminution in swing while the patient is walking
2	Obvious diminution in swing suggesting shoulder rigidity
3	Stiff gait with little or no arm swing noticeable
4	Rigid gait with arms slightly pronated; or stooped-shuffling gait with propulsion and retropulsion
2.	**ARM DROPPING** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides, in a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly.
0	Normal, free fall with loud slap and rebound
1	Fall slowed slightly with less audible contact and little rebound
2	Fall slowed, no rebound
3	Marked slowing, no slap at all
4	Arms fall as though against resistance; as though through glue
3.	**SHOULDER SHAKING** The subject's arms are bent at a right angle at the elbow and taken one at a time by the examiner who grabs one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and from and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
4.	**ELBOW RIGIDITY** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to the procedure is rated. (The presence of cogwheel rigidity is noted separately.)
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint

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5.	**WRIST RIGIDITY** The wrist is held in one hand and then the fingers held by the examiner's other hand with the wrist moved to extension, and both ulnar and radial deviation. The resistance to this procedure is rated:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
6.	**HEAD ROTATION** The patient sits or stands and is told that you are going to move his head from side to side, that it will not hurt and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the patient's head between the two hands with fingers on back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to the movement.
0	Loose, no resistance
1	Slight resistance to movement although the time to rotate may be normal
2	Resistance is apparent and time of rotation is slowed
3	Resistance is obvious and rotation is slowed
4	Head appears stiff and rotation is difficult to carry out
7.	**GLABELLA TAP** Subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
0	0-5 blinks
1	6-10 blinks
2	11-15 blinks
3	16-20 blinks
4	21 and more blinks
8.	**TREMOR** Patient is observed walking into examining room and then is examined for this item.
0	Normal
1	Mild finger tremor, obvious to sight and touch
2	Tremor of hand or arm occurring spasmodically
3	Persistent tremor of one or more limbs
4	Whole body tremor
9.	**SALIVATION** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
0	Normal
1	Excess salivation so that pooling takes place if the mouth is open and the tongue raised
2	Excess salivation is present and might occasionally result in difficulty in speaking
3	Speaking with difficulty because of excess salivation
4	Frank drooling

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10.	**AKATHISIA** Patient is observed for restlessness. If restlessness is noted, ask: "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring but patient report can help make the assessment.
0	No restlessness reported or observed
1	Mild restlessness observed
2	Moderate restlessness observed
3	Restlessness is frequently observed
4	Restlessness persistently observed

Adapted and used with permission. Reference: Simpson GN, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica. 1970;45(suppl 212):11-9.

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Appendix 18 Baseline Columbia-Suicide Severity Rating Scale

Protocol 331-201-00061

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.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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 Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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	**Lifetime: Time He/She Felt Most Suicidal**	**Past 90 Days**
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

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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). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past 6 Months ***- Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
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 (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** 1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (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 (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped 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 (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (2) Mostly to get attention, revenge or a reaction from others. (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (0) Does not apply		

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 1 year**
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** ☐ ☐	**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 _____	**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** ☐ ☐

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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* _____

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Appendix 19 Since Last Visit Columbia-Suicide Severity Rating Scale

Protocol 331-201-00061

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.

Disclaimer:

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

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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 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 ☐
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 ☐
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 ☐
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 ☐
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 ☐

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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 Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
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	____

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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 ☐

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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* _____

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Appendix 20 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 7 Jun 2017

PURPOSE:

The sponsor has determined the need for a formal amendment to the original protocol approved on 29 Sep 2016 to:

- Specify the trial treatment dosing schedule and dosing rules.
- Clarify index traumatic event and traumatic brain injury exclusion criteria.
- Clarify the date for calculation of medical history exclusions and concomitant medication washout.
- Add exclusion for history of bariatric surgery, due to concern for pharmacokinetic effects.
- Clarify the requirement for contact with the medical monitor in cases of obesity.
- Exclude the males who refuse to abstain from donating sperm during the trial and for 30 days after the last dose of IMP.
- Provide for additional extensions of the screening period.
- Clarify the visit windows in the Schedule of Assessments.
- Add review of birth control methods to Schedule of Assessments.
- Change start of wearable device from Screening Visit to Baseline (Day 0) Visit.
- Clarify that first dose is to be given on the day after the Baseline (Day 0) Visit.
- Clarify process for review of electronic report of labs and ECG.
- Clarify/add/update lab sample collection.
- Include prazosin in list of restricted concomitant medications.
- Clarify follow-up requirements for adverse events and IREs.
- Add the collection of FBR sample.

In addition, changes to text to enhance readability and consistency and to correct typographical, punctuation, and formatting errors. These changes were minor and do not change the design or content of the protocol, and therefore, are not summarized in this appendix.

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BACKGROUND:

This amendment was introduced to correct various administrative errors, to clarify language that proved to be unclear and to add lab tests to be consistent with other brexpiprazole trials past and ongoing.

MODIFICATIONS TO PROTOCOL:

General Revisions:

Following global changes were made to the protocol:

- Replaced all occurrences of interactive voice response system (IVRS)/interactive web response system (IWRS) or equivalent with interactive response technology (IRT).
- Added DNA, FBR, LDL, HDL, and IRT to the list of abbreviations and deleted IVRS/IWRS.
- Removed registering the trial site visits and blister card assignments using IRT from Screening, Baseline (Day 0), Week 1, Week 2, Week 3, Week 4, Week 6, Week 8, Week 10, and End of Week 12/ET, as applicable.
- Revised to provide wearable device at the Baseline (Day 0) Visit, not at the Screening Visit.
- Prolactin "which is part of serum chemistry" is the only blinded clinical laboratory test. Therefore, it was parted from other tests using a square bracket: "Serum chemistry [including blinded prolactin]".
- Added future biospecimen research sample collection to Week 6 Visit.
- Revised Appendix 7 to add Chapter 4 for SOT.
- Revised Appendix 12 to add LEC-5 extended version.
- Revised Appendix 13 to add M.I.N.I. Version 7.0.2.
- Revised Appendix 18 to add Past 90 days and Past 1 year in the right hand column.

Sectional Revisions:

Location	Old Text	Updated Text
Synopsis, Trial design	*Screening Phase:* The screening period will be 14 days and will begin when consent has been obtained. An extension of up to 14 additional days (28-day maximum total) can be requested from the medical monitor, if needed to meet eligibility requirements. An interactive voice response system (IVRS)/interactive web response system (IWRS) will be used to obtain an identification (ID) number for each subject with documented consent. [not consecutive]	*Screening Phase*: The screening period will be **up to** 14 days and will begin when consent has been obtained. **Additional** extension**(s)** of up to 14 additional days can be requested from the medical monitor, if needed to meet eligibility requirements. An **eSource method** will be used to obtain an identification (ID) number for each subject with documented consent.

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Location	Old Text	Updated Text
	Follow-up: If any subject discontinues the trial early, every effort should be made to complete the Week 12/early termination (ET) evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or clinic visit for 14 (+ 2) days after the last dose of investigational medicinal product (IMP). Any subject who withdraws because of a serious adverse event (SAE) should be seen in the clinic, if possible.	[not consecutive] *Follow-up:* If any subject discontinues the trial early, every effort should be made to complete the Week 12/early termination (ET) evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or clinic visit**,** 14 (+ 2) days after the last dose of investigational medicinal product (IMP). Any subject who withdraws because of a serious adverse event (SAE) should be seen in the clinic, if possible.
Synopsis, Inclusion/ Exclusion Criteria	Key Exclusion Criteria: 1) Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. 5) Initial onset of trauma occurred before age 16. 14) Subjects who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) or other neurological disorders or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning. 15) Subjects who have experienced a traumatic event with 3 months of screening 17) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days). 18) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular,	Key Exclusion Criteria: 1) Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. **Males who do not agree to abstain from sperm donation during the trial and for 30 days after the last dose of IMP.** 5) **The index traumatic event** occurred before age 16. 14) Subjects who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) or other neurological disorders or systemic medical diseases **where the traumatic brain injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact patient safety, in the investigator's opinion.** 15) Subjects who have experienced a traumatic event with**in** 3 months of screening. 17) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at

Location	Old Text	Updated Text
	pulmonary, or gastrointestinal disorders, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevated to > 2 × the upper limit of normal [ULN]). Medical conditions that are minor or well‑controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.	least the past 90 days **prior to the Baseline [Day 0] Visit**). 18) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevated to > 2 × the upper limit of normal [ULN])**, or bariatric surgeries that may cause malabsorption**. Medical conditions that are minor or well‑controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.
Synopsis, Criteria for Evaluation	Safety Endpoints: Standard safety variables will include AEs, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin and HbA1c], and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference will also be measured.	Safety Endpoints: Standard safety variables will include AEs, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin**],** HbA1c**,** and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference will also be measured.
Section 3.1 Type/Design of Trial	*Screening Phase:* The screening period will be 14 days and will begin when consent has been obtained. An extension of up to 14 additional days (28-day maximum total) can be requested from the medical monitor, if needed to meet eligibility requirements. An interactive response system (IVRS)/interactive web response system (IWRS) will be used to obtain an identification (ID) number for each subject with documented consent. Subjects will be between 18 and 65 years of age, inclusive, at the time of screening and will have a diagnosis of PTSD as defined by DSM 5	*Screening Phase:* The screening period will be **up to** 14 days and will begin when consent has been obtained. **Additional** extension**(s)** of up to 14 additional days can be requested from the medical monitor, if needed to meet eligibility requirements. An **eSource method** will be used to obtain an identification (ID) number for each subject with documented consent. Subjects will be between 18 and 65 years of age, inclusive, at the time of screening and will have a diagnosis of PTSD as defined by DSM-5 criteria. All subjects must agree to discontinue all

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Location	Old Text	Updated Text
	criteria. All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. *Follow-up:* If any subject discontinues the trial early, every effort should be made to complete the Week 12/early termination (ET) evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or clinic visit for 14 (+ 2) days after the last dose of investigational medicinal product (IMP). Any subject who withdraws because of a serious adverse event (SAE) should be seen in the clinic, if possible.	prohibited medications during the screening period in order to meet the protocol-specified washout periods. *Follow-up:* If any subject discontinues the trial early, every effort should be made to complete the Week 12/early termination (ET) evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or clinic visit**,** 14 (+ 2) days after the last dose of investigational medicinal product (IMP). Any subject who withdraws because of a serious adverse event (SAE) should be seen in the clinic, if possible.
Section 3.2 Trial Treatments	During the double-blind treatment phase, subjects will receive IMP, consisting of brexpiprazole monotherapy, brexpiprazole + Zoloft (sertraline), Zoloft (sertraline) monotherapy, or placebo, depending on the subject's treatment assignment. All doses of IMP should be taken together at the same time each day, if possible. All doses of IMP can be taken without regard to meals. If tolerability issues arise, the timing of administration of the IMP may be adjusted at the investigator's discretion in order to achieve optimum tolerability and compliance.	**During the first 3 weeks of the trial, subjects will be titrated according to the blinded titration schedule, based on the treatment group to which they will be randomized. Per this schedule, at Week 3, subjects will receive:** **1) Brexpiprazole monotherapy 2 mg/day; or** **2) Brexpiprazole 2 mg/day + Zoloft (sertraline) 150 mg/day; or** **3) Zoloft (sertraline) monotherapy 150 mg/day; or** **4) Placebo.** **No dose adjustments are allowed during the 3 week titration period, thus any subject unable to tolerate the assigned dose of IMP during the titration period must be withdrawn from the trial. Once the subject takes the first dose following the forced titration period, the dose of IMP can be adjusted to optimize efficacy and safety/tolerability according to the following rules:** • **Dose <u>increases</u> can occur only at the Week 4 visit.** • **Dose decreases can occur at scheduled or unscheduled visits starting after the first dose following Week 3 and are not**

Location	Old Text	Updated Text
		allowed after the Week 6 visit. • **Dose may be maintained, decreased (if not decreased already) or increased at the Week 4 visit. No further dose increases are permitted after Week 4.** • **Dose decreases will be allowed between Week 3 (following the first post-visit dose as above) and Week 6, if there are tolerability issues.** • **Dose must be maintained for the remainder of the treatment period after Week 6.** • **If subjects are unable to maintain the Week 6 dose due to tolerability issues, the subject must be withdrawn from the trial.** All doses of IMP should be taken together at the same time each day, if possible. All doses of IMP can be taken without regard to meals. If tolerability issues arise, the timing of administration of the IMP may be adjusted at the investigator's discretion in order to achieve optimum tolerability and compliance.
Section 3.3.2 Subject Selection and Numbering	At screening, subjects will be assigned a unique subject ID number upon completion of the consent process based on sequential enrollment in the trial. Subjects will be assigned a unique subject number upon enrollment/randomization.	At screening, subjects will be assigned a unique subject ID number upon completion of the consent process based on sequential enrollment in the trial.
Section 3.4.3 Exclusion Criteria:	Table 3.4.3-1 Exclusion Criteria Sex and Reproductive Status 1) Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.	Table 3.4.3-1 Exclusion Criteria Sex and Reproductive Status 1) Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. **Males who do not agree to abstain from sperm donation during the trial**

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Location	Old Text	Updated Text
	Target Disease 5) Initial onset of trauma occurred before age 16. 14) Subjects who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) or other neurological disorders or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning. 15) Subjects who have experienced a traumatic event with 3 months of screening. Medical History and Concurrent Diseases 17) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days). 18) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of ischemic heart disease, myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and AST or ALT elevated to > 2 × ULN). Medical conditions that are minor or well‑controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a	**and for 30 days after the last dose of IMP.** Target Disease **5) The index traumatic event** occurred before age 16. 14) Subjects who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) or other neurological disorders or systemic medical diseases **where the traumatic brain injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact patient safety, in the investigator's opinion.** 15) Subjects who have experienced a traumatic event with**in** 3 months of screening. Medical History and Concurrent Diseases 17) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days **prior to the Baseline [Day 0] Visit**). 18) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as ischemic heart disease, myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and AST or ALT elevated to > 2 × ULN)**, or bariatric surgeries that may cause malabsorption**. Medical conditions that are minor or well‑controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted

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	corresponding high BMI, need to be reviewed and discussed with the medical monitor. [not consecutive] Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months. [not consecutive] Screen failures excluded may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, a 14-day extension of screening (28-day maximum total) may be requested from the medical monitor. This extension should be requested prior to the expiration of the 14-day screening period. If no extension is granted, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. Subjects may be rescreened twice for this trial.	in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a corresponding high BMI **(BMI ≥ 40 kg/m^2)**, need to be reviewed and discussed with the medical monitor. [not consecutive] Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months **with no menses without an alternative medical cause**. [not consecutive] Screen failures **due to** exclu**sionary criteria** may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, **additional** 14-day extension**(s)** of screening may be requested from the medical monitor. **Any** extension should be requested prior to the expiration of the **previous extension or** screening period, **as applicable**. If no extension is granted, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. Subjects may be rescreened twice for this trial.
3.5.3 Safety Endpoints	Standard safety variables will include adverse events (AEs), clinical laboratory tests (hematology, serum chemistry [including blinded prolactin glycosylated hemoglobin (HbA1c)], and urinalysis), physical examinations, vital sign measurements, and electrocardiograms (ECGs). Body weight, height, and waist circumference will also be measured.	Standard safety variables will include adverse events (AEs), clinical laboratory tests (hematology, serum chemistry [including blinded prolactin**],** glycosylated hemoglobin **[**HbA1c**]**, and urinalysis), physical examinations, vital sign measurements, and electrocardiograms (ECGs). Body weight, height, and waist circumference will also be measured.

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Old Text: Table 3.7-1 Schedule of Assessment

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit	Week 2 Visit	Week 3 Visit	Week 4 Visit	Week 6 Visit	Week 8 Visit	Week 10 Visit	Week 12/ ET[b] Visit	Post-treatment Follow-up[c]
ENTRANCE CRITERIA											
Informed Consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical history	X										
Psychiatric history including PTSD history	X										
MINI	X										
PTSD treatments: pharmacological and non-pharmacological and E-TRIP	X										
Prior medication washout[d]	X										
LEC-5	X										
OSU TBI-ID	X										
HIV, HBsAg, and anti-HCV	X										
EFFICACY											
CAPS-5[e]	X	X	X		X		X		X	X	
SOTS		X				X				X	
CGI-S		X	X	X	X	X	X	X	X	X	
PCL-5		X	X		X		X		X	X	
HADS		X	X		X		X		X	X	
Wearable device[f]	X ---------- X										
SAFETY											
Assess need for double-blind IMP dose modification						X	X				

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Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit	Week 2 Visit	Week 3 Visit	Week 4 Visit	Week 6 Visit	Week 8 Visit	Week 10 Visit	Week 12/ ET[b] Visit	Post-treatment Follow-up[c]
Physical examination[g]	X									X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[i]	X	X								X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis), including blinded prolactin and TSH[j]	X	X[k]					X			X	
HbA1c	X									X	
Urine drug screen/blood alcohol[l]	X									X	
Urine pregnancy test[m]	X	X				X		X		X	
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	
SAS		X		X			X			X	
AIMS		X		X			X			X	
BARS		X		X			X			X	
Adverse events[o]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[p]		X	X	X	X	X	X	X	X	X	X
OTHER											
Register visit in IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	
Drug dispensing		X	X	X	X	X	X	X	X		
Drug accountability			X	X	X	X	X	X	X	X	
Pharmacokinetic and Pharmacogenomic Sampling											
PK sample[q]							X			X	
Pharmacogenomic sample[r]							X				

anti-HCV = antibodies to hepatitis C virus; E-TRIP = Emory Treatment Resistance Interview for PTSD; HBsAg = hepatitis B surface antigen; LEC-5 = Life Events Checklist for DSM-5; TSH = thyroid-stimulating hormone.

[a]Screening begins upon completion of the consent process. Although the screening period takes place between Day −14 and Day −3 prior to enrollment, subjects will participate in screening activities for a minimum of 3 days. Therefore, screening procedures should be initiated immediately. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, a 14-day extension of screening (28-day maximum total) may be requested from the medical monitor. This extension should be requested prior to the expiration of the 14-day screening period.

[b]If a subject discontinues early, every effort should be made to complete the "End of Week 12/ET" evaluations as soon as possible and whenever possible prior to starting any new medication or treatment.

[c]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety.

[d]Washout of prohibited medications begins after completion of the consent process and must comply with the required washout periods in Section 4.1.

[e]The CAPS-5 Past Month version will be completed for all subjects at screening to determine eligibility and the CAPS-5 Past Week version will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial. The CAPS-5 Past Week version will also be completed at all visits after the Baseline (Day 0) Visit when the assessment is scheduled for collection.

[f]After completion of the consent process during the Screening Visit, the wearable device will be put on the subject's nondominant wrist, whenever possible, and worn daily until Week12/ET.

[g]To include measurement of height (at screening only) and waist circumference.

[h]Vital sign measurements include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine and standing after the subject has been in each position for at least 3 minutes.

[i]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated in triplicate to confirm the finding(s) before excluding the subject from the trial (see Section 3.7.3.4). A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis.

[j]Blood samples for clinical laboratory tests should be drawn after a minimum 8-hour fast and should be drawn after a minimum 8-hour fast at screening, if possible.

[k]If a fasting blood sample was obtained at the Screening Visit and less than 10 days have elapsed since the Screening Visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the Baseline (Day 0) Visit.

[l]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator (Section 4.2.2.2). See Section 3.4.3 for exclusions based on urine drug screen and blood alcohol tests at screening and baseline requirements based on urine drug screen and blood alcohol results.

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[m]For women of childbearing potential only (WOCBP). All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[n]The "Baseline/Screening" C-SSRS form will be completed for all subjects at screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at all visits after the Baseline (Day 0) Visit.

[o]Adverse events will be recorded starting after the subject completes the consent process.

[p]All prescription and non-prescription medications taken during the trial will be recorded. Details of prohibited medications are provided in Section 4.

[q]A PK sample will be collected at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling.

[r]A pharmacogenomics sample to assess the CYP2D6 metabolism status will also be collected.

New Text: Table 3.7-1 Schedule of Assessment

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
ENTRANCE CRITERIA											
Informed Consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical history	X										
Psychiatric history including PTSD history	X										
MINI	X										
PTSD treatments: pharmacological and non-pharmacological and E-TRIP	X										
Prior medication washout[d]	X										
LEC-5	X										
OSU TBI-ID	X										
HIV, HBsAg, and anti-HCV	X										
Review of birth control methods	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
EFFICACY											
CAPS-5[e]	X	X	X		X		X		X	X	
SOTS		X				X				X	
CGI-S		X	X	X	X	X	X	X	X	X	
PCL-5		X	X		X		X		X	X	
HADS		X	X		X		X		X	X	
Wearable device[f]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
SAFETY											
Assess need for double-blind IMP dose modification						X	X				
Physical examination[g]	X									X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[i]	X	X								X	
Clinical laboratory tests (hematology, serum chemistry **[including blinded prolactin]**, urinalysis), TSH[j]	X	X[k]					X			X	
HbA1c	X									X	
Insulin	**X**	**X[k]**								**X**	
Urine drug screen/blood alcohol[l]	X									X	
Urine pregnancy test[m]	X	X				X		X		X	
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	
SAS		X		X			X			X	
AIMS		X		X			X			X	
BARS		X		X			X			X	
Adverse events[o]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[p]		X	X	X	X	X	X	X	X	X	X
OTHER											
Drug dispensing[q]		X	X	X	X	X	X	X	X		

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Table 3.7-1 Schedule of Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
Drug accountability			X	X	X	X	X	X	X	X	
Pharmacokinetic and Pharmacogenomic Sampling											
PK sample[r]							X			X	
Pharmacogenomic sample[s]							X				
FBR sample[t]							X				

anti-HCV = antibodies to hepatitis C virus; E-TRIP = Emory Treatment Resistance Interview for PTSD; **FBR = future biospecimen research**; HBsAg = hepatitis B surface antigen; LEC-5 = Life Events Checklist for DSM-5; TSH = thyroid-stimulating hormone.

[a]Screening begins upon completion of the consent process. Although the screening period takes place between Day −14 and Day −3 prior to enrollment, subjects will participate in screening activities for a minimum of 3 days. **It is requested to complete screening as quickly as possible**. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, **additional** 14-day extension**(s)** of screening may be requested from the medical monitor. **Any** extension should be requested prior to the expiration of the **previous extension or** screening period**, as applicable**.

[b]If a subject discontinues early, every effort should be made to complete the "End of Week 12/ET" evaluations as soon as possible and whenever possible prior to starting any new medication or treatment.

[c]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety.

[d]Washout of prohibited medications begins after completion of the consent process and must comply with the required washout periods in Section 4.1.

[e]The CAPS-5 Past Month version will be completed for all subjects at screening to determine eligibility and the CAPS-5 Past Week version will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial. The CAPS-5 Past Week version will also be completed at all visits after the Baseline (Day 0) Visit when the assessment is scheduled for collection.

[f]The wearable device will be put on the subject's nondominant wrist, whenever possible, **at the Baseline (Day 0) Visit** and worn daily until Week12/ET. **The trial site will download Actigraphy data during each subject visit.**

[g]To include measurement of height (at screening only) and waist circumference.

[h]Vital sign measurements include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine and standing after the subject has been in each position for at least 3 minutes.

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[i]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated in triplicate to confirm the finding(s) before excluding the subject from the trial (see Section 3.7.3.4). A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis.

[j]Blood samples for clinical laboratory tests should be drawn after a minimum 8-hour fast **at the Baseline (Day 0) Visit** and should be drawn after a minimum 8-hour fast at screening, if possible. **If blood draws are not part of the site's SOP, the subject should not be asked to fast for the study prior to signing the ICF.**

[k]If a fasting blood sample was **not** obtained at the Screening Visit and **if more than** 10 days have elapsed since the Screening Visit, clinical laboratory tests (**hematology, serum chemistry [including blinded prolactin], TSH with reflex to T4 if the result for TSH is abnormal, insulin, and urinalysis)** need to be repeated at the Baseline (Day 0) Visit.

[l]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator (Section 4.2.2.2). See Section 3.4.3 for exclusions based on urine drug screen and blood alcohol tests at screening and baseline requirements based on urine drug screen and blood alcohol results.

[m]For women of childbearing potential only (WOCBP). All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[n]The "Baseline/Screening" C-SSRS form will be completed for all subjects at screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at all visits after the Baseline (Day 0) Visit.

[o]Adverse events will be recorded starting after the subject completes the consent process.

[p]All prescription and non-prescription medications taken during the trial will be recorded. Details of prohibited medications are provided in Section 4.

[q]The subject will be instructed to take their first dose the day after the Baseline (Day 0) Visit (see Section 3.7.1.2).

[r]A PK sample will be collected at the same time of collection of clinical labs. Time of last 3 doses will be recorded at the time of PK sampling.

[s]A pharmacogenomics sample to assess the CYP2D6 metabolism status will also be collected.

[t]FBR sample will be collected if subject consent is received and if allowed by IRB/IEC (see Section 3.7.5).

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Location	Old Text	Updated Text
Section 3.7.1.1 Screening	The screening period begins after consent has been obtained. Although the screening period takes place between Day −14 and Day −3, subjects will participate in screening activities for a minimum of 3 days. In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, a 14-day extension of screening (28 day maximum total) may be requested from the medical monitor. This extension should be requested prior to the expiration of the 14-day screening period. After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing the IVRS/IWRS or equivalent. Completion of screening activities may require more than one visit; however, only the initial visit will be registered in the IVRS/IWRS or equivalent. Screening evaluations will include the following: [not consecutive] • Blood samples for clinical laboratory tests (hematology and serum chemistry, including blinded prolactin, HbA1c, and thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T4] if the result for TSH is abnormal) should be drawn after a minimum 8 hour fast at screening. See Table 3.4.3-1 for exclusions based on outcome of screening clinical laboratory tests.	The screening period begins after consent has been obtained. Although the screening period takes place between Day −14 and Day −3, subjects will participate in screening activities for a minimum of 3 days. **It is requested to complete screening as quickly as possible.** In the event that a subject cannot be randomized prior to expiration of the 14-day screening period, **additional** 14-day extension**(s)** of screening may be requested from the medical monitor. **Any** extension should be requested prior to the expiration of the **previous extension or** screening period**, as applicable**. After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing **eSource**. Completion of screening activities may require more than one visit; however, only the initial visit will be registered in the **eSource**. Screening evaluations will include the following: [not consecutive] • Blood samples for clinical laboratory tests (hematology**,** serum chemistry **[**including blinded prolactin**]**, HbA1c, thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T_4] if the result for TSH is abnormal**, insulin, and urinalysis**) should be drawn after a minimum 8-hour fast at screening. See Table 3.4.3-1 for exclusions based on outcome of screening clinical laboratory tests.
Section 3.7.1.2 Baseline (Day 0) Visit	• If a fasting blood sample was obtained at the Screening Visit and more than 10 days have elapsed since the Screening Visit, blood samples for clinical laboratory tests (hematology and serum chemistry, including blinded prolactin, HbA1c, and TSH with reflex to T4 if the result for TSH is abnormal) should be drawn after a minimum 8-hour fast at Baseline (Day 0). [not consecutive] • Trial personnel will access the IVRS/IWRS or equivalent to register the visit and to obtain blister card assignment(s) for double-blind IMP. The assigned IMP will be dispensed to the	• If a fasting blood sample was **not** obtained at the Screening Visit and **if** more than 10 days have elapsed since the Screening Visit, blood samples for clinical laboratory tests (hematology and serum chemistry **[**including blinded prolactin**]**, TSH with reflex to T_4 if the result for TSH is abnormal, **insulin, and urinalysis**) should be drawn after a minimum 8-hour fast at Baseline (Day 0) **Visit**. [not consecutive] • The assigned IMP will be dispensed to the subject. **The subjects should be instructed to take their first dose the day after the Baseline (Day 0) Visit.** • The wearable device will be **put on**

Location	Old Text	Updated Text
	subject. • The wearable device will be taken off and the data will be downloaded to the computer, prior to putting the device back on to continue recording.	**subject's nondominant wrist. The wearable device will be worn continuously throughout the double-blind treatment period.**
Section 3.7.1.7 Treatment Phase - Week 6	[not consecutive] Blood samples for clinical laboratory tests (hematology and serum chemistry, including blinded prolactin) should be drawn after a minimum of 8-hours fasting.	[not consecutive] Blood samples for clinical laboratory tests (hematology**,** serum chemistry **[**including blinded prolactin**], TSH with reflex to T_4 if the result for TSH is abnormal, and urinalysis**) should be drawn after a minimum of 8-**hour** fasting.
Section 3.7.1.10 End of Week 12/Early Termination	[not consecutive] Blood samples for clinical laboratory tests (hematology, HbA1c, and serum chemistry, including blinded prolactin) and blood alcohol testing should be drawn after a minimum 8-hour fast at Week 12/ET.	[not consecutive] Blood samples for clinical laboratory tests (hematology, HbA1c, serum chemistry [including blinded prolactin**]**, **TSH with reflex to T_4 if the result for TSH is abnormal, insulin, and urinalysis**) and blood alcohol testing should be drawn after a minimum 8-hour fast at Week 12/ET.
Section 3.7.1.11 Post-Treatment Follow-up Period	Subjects will be contacted to monitor for safety events via telephone contact or clinic visit (investigator's discretion) for 14 (+ 2) days after the last dose of IMP. Adverse events and concomitant medications will be recorded. This contact also applies to subjects withdrawn prematurely from the trial.	Subjects will be contacted to monitor for safety events via telephone contact or clinic visit (investigator's discretion)**,** 14 (+ 2) days after the last dose of IMP. Adverse events and concomitant medications will be recorded. This contact also applies to subjects withdrawn prematurely from the trial.
Section 3.7.2.6 Wearable Device	The wearable device should be put on the subject's nondominant wrist, whenever possible. The wearable device will be worn continuously throughout the double-blind treatment period. At each trial visit, the wearable device is taken off and the data will be downloaded to the computer. At the Week 12/ET Visit, the wearable device monitoring will be stopped.	**Use of the wearable device is optional and does not require a separate consent form. If the subject agrees to its use, the wearable device should be put on the subject's nondominant wrist at the Baseline (Day 0) Visit. The wearable device is to be worn continuously throughout the double-blind treatment period. At each trial visit, the wearable device is taken off, the data will be downloaded to the computer and the device will be placed back on the subject's nondominant wrist. At the Week 12/ET Visit, the wearable device monitoring will be stopped and the device returned to the trial site. All data from device should be transferred to Phillips by the conclusion of the Week 12/ET Visit.**
Section 3.7.3.2 Clinical Laboratory Assessment	A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if	A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if

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Location	Old Text	Updated Text
	needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. If a fasting blood sample was obtained at the Screening Visit and less than 10 days have elapsed since the Screening Visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the Baseline (Day 0) Visit. The results of these tests at screening must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically. [not consecutive] The total volume of blood to be collected during the trial is expected to be approximately 160 mL.	needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. If a fasting blood sample was **not** obtained at the Screening Visit and **if more than** 10 days have elapsed since the Screening Visit, clinical laboratory tests **(hematology, serum chemistry [including blinded prolactin], HbA1c, TSH with reflex to T4 if the result for TSH is abnormal, insulin, and urinalysis)** need to be repeated at the Baseline (Day 0) Visit. The results of these tests at screening must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory **will be retained electronically within the lab vendor's online portal and assessed by the investigator or qualified designee for clinical significance within eSource.** [no consecutive] The total volume of blood to be collected during the trial is expected to be approximately **100 - 115** mL.

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Old Text: Table 3.7.3.2-1 Clinical Laboratory Assessment

Table 3.7.3.2-1 Clinical Laboratory Assessments	
Hematology: Hemoglobin MCHC MCV RBC count WBC count with differential Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity Additional Tests (screening only): HIV HBsAg Anti-HCV	Serum Chemistry: ALP ALT AST Bilirubin, total BUN Calcium Cholesterol CPK Creatinine GGT Glucose LDH Potassium Prolactin[a] Protein, total Sodium Triglycerides Additional Tests: Urine pregnancy for WOCBP TSH HbA1c

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; LDH = lactic dehydrogenase; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

[a]Prolactin results will be blinded to the investigators and trial staff.

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New Text: Table 3.7.3.2-1 Clinical Laboratory Assessment

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin **Hematocrit** MCHC MCV RBC count WBC count with differential **Platelet count** Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity **Ketones** **Urine Drug Screens:** **Amphetamines/MDMA** **Barbiturates** **Benzodiazepines** **Cannabinoids** **Cocaine** **Methadone** **Opiates** **Phencyclidine** **Propoxyphene** **Drug and alcohol Screening** **Blood alcohol**	Serum Chemistry: ALP ALT AST Bilirubin, total BUN Calcium Cholesterol **(total, LDL, and HDL)** CPK Creatinine GGT Glucose LDH Potassium Prolactin[a] Protein, total Sodium Triglycerides **Insulin** **Chloride** **Magnesium** **Bicarbonate** **Inorganic phosphorus** **Uric acid** **Albumin** Additional Tests: Urine pregnancy for WOCBP TSH HbA1c Additional Tests (screening only): HIV HBsAg Anti-HCV

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; **HDL = high density lipoprotein;** LDH = lactic dehydrogenase; **LDL = low density lipoprotein;** MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; **MDMA = methylenedioxymethamphetamine**; WBC = white blood cell.

[a]Prolactin results will be blinded to the investigators and trial staff.

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Location	Old Text	Updated Text
Section 3.7.3.4 Electrocardiogram Assessments	All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial.	All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. **The principal investigator or qualified designee will review the ECG tracing and cardiology report within the central ECG vendor's online portal, assess the findings, noting whether or not any abnormal results are clinically significant within eSource.**
Section 3.7.3.5.4 Columbia-Suicide Severity Rating Scale	Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "baseline/screening" and "Since Last Visit" versions of the scale. The "baseline/screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject with active suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Table 3.4.3-1). The "Since Last Visit" C-SSRS form will also be completed at all visits after screening. Copies of the C-SSRS forms are provided in Appendix 18 and Appendix 19.	Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "baseline/screening" and "Since Last Visit" versions of the scale. The "baseline/screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Table 3.4.3-1). The "Since Last Visit" C-SSRS form will also be completed at all visits after screening. Copies of the C-SSRS forms are provided in Appendix 18 and Appendix 19.
Section 3.7.3.5.5	Pharmacogenomic Testing A pharmacogenomics sample to assess the CYP2D6 metabolism status will be collected at Week 6. All samples will be shipped to the pharmacogenomics laboratory. Detailed handling and shipping instructions are provided in Appendix 1.	**Deoxyribonucleic Acid (DNA) Blood Samples for** Pharmacogenomic Testing **A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7 1) in order to extract deoxyribonucleic acid (DNA) and determine genotypes and related phenotypes for CYP2D6. The method used to determine these genotypes also generates genotype data for additional genes related to absorption, distribution, metabolism, and excretion (ADME) of the compound. Phenotyping of these additional genes is not currently planned**

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Location	Old Text	Updated Text
		but may be considered in the future. All samples will be shipped to the central lab provided in Appendix 1.
Section 3.7.5 Future Biospecimen Research	New section for this amendment. Hence the previous Section 3.7.5 End of Trial is now Section 3.7.6. A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7 1) from consenting subjects, and if allowed by the IRB/IEC. Research performed on this sample may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. Processing, storage, and shipping instructions for FBR samples are provided in Appendix 1.	
Section 3.8.3.3 Documenting Reasons for Treatment Interruption/ Discontinuati-on	• Withdrawal of informed consent (complete written withdrawal of consent form)	• Withdrawal of informed consent
Section 3.9 Screen Failures	Screen failures excluded may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 14 day screening period, a 14-day extension of screening (28-day maximum total) may be requested from the medical monitor. This extension should be requested prior to the expiration of the 14-day screening period.	Screen failures **due to** exclu**sionary criteria** may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 14 day screening period, **additional** 14-day extension**(s)** of screening may be requested from the medical monitor. **Any** should be requested prior to the expiration of the **previous extension** screening period**, as applicable**.

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Old Text: Table 4.1-2 List of Medications Prohibited/Restricted During the Trial

Table 4.1-2 List of Medications Prohibited/Restricted During the Trial	
1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Anticonvulsants c) Antidepressants d) Mood stabilizers (ie, lithium) e) Benzodiazepines, except when used to manage TEAEs such as agitation and anxiety[a] f) Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage TEAEs related to insomnia[b] g) Stimulants and atomoxetine – allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to screening. Should be continued throughout trial participation. h) Opioid analgesics, unless approval is obtained from the medical monitor. Approval for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, etc) j) Disulfiram

[not consecutive]

[b]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of insomnia for up to 4 days per week, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eSource

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New Text: Table 4.1-2 List of Medications Prohibited/Restricted During the Trial

Table 4.1-2 List of Medications Prohibited/Restricted During the Trial
All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Anticonvulsants c) Antidepressants d) Mood stabilizers (ie, lithium) e) Benzodiazepines, except when used to manage TEAEs such as agitation and anxiety[a] f) Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage TEAEs related to insomnia[b] g) Stimulants and atomoxetine – allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to **Baseline (Day 0) Visit**. Should be continued throughout trial participation h) Opioid analgesics, unless approval is obtained from the medical monitor. Approval for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, etc) j) Disulfiram k) **Prazosin - allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to Baseline (Day 0) Visit. Should be continued throughout trial participation**

[not consecutive]

[b]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of **TEAEs related to** insomnia for up to 4 days per week, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eSource.

Location	Old Text	Updated Text
Section 4.2.1 Restricted Therapies and Precautions	Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of TEAEs related to insomnia for up to 4 days per week total during the treatment period, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication and the prescribing information is to be used to	Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of **TEAEs related to** insomnia for up to 4 days per week total during the treatment period, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication and the prescribing information is to be used to

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Location	Old Text	Updated Text
	determine the maximum allowable daily dose for the treatment of insomnia.	determine the maximum allowable daily dose for the treatment of insomnia.
Section 5.3 Immediately Reportable Events	The investigator must immediately report after either the investigator or site personnel become aware of any SAE, DILI, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource.)	The investigator must immediately report after either the investigator or site personnel become aware of any SAE, **AE related to occupational exposure,** DILI, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource.)
Section 5.5 Pregnancy	Women of childbearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months). For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.	Women of childbearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months **with no menses without an alternative medical cause**). For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months **with no menses without an alternative medical cause**; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.
Section 5.7 Follow-up of Adverse Events	Delete: For this trial, information on AEs will be followed for up to 14 (+ 2) days after the last dose of IMP has been administered.	
Section 5.7.1 Follow-up of	Nonserious AEs that are identified at any time during the trial must be recorded on	Nonserious AEs that are identified at any time during the trial must be recorded on

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Location	Old Text	Updated Text
Nonserious Adverse Events	the AE eSource with the current status noted. If a subject has an AE or has not recovered from an AE at the last scheduled contact, follow-up contacts will be scheduled at least every 4 weeks until resolution of the AE is confirmed or the condition is considered clinically stable. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).	the AE eSource with the current status **(ongoing or resolved/recovered)** noted. All nonserious events **(that are not IREs)** that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested **by the sponsor** to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).
Section 5.7.2	Follow-up of Serious Adverse Events This trial requires that subjects be actively monitored for SAEs up to 14 (+ 2) days after the last dose of IMP is administered. Serious AEs **that are identified or ongoing at the last scheduled contact** must be recorded on the AE eSource page and reported to the sponsor according to the reporting procedures outlined in Section 5.3. This may include unresolved previously reported SAEs, or new SAEs. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has been resolved, stabilized, or the subject is lost to follow-up.	Follow-up of Serious Adverse Events **and Immediately Reportable Events** This trial requires that subjects be actively monitored for SAEs **and IREs** up to 14 (+ 2) days after the last dose of IMP is administered. Serious AEs **and nonserious IREs** that are identified or ongoing at the last scheduled contact must be recorded **as such** on the AE eSource page. **If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eSource page according to the appropriate reporting procedures.** The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up **or has died**. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has been resolved, stabilized, or the subject is lost to follow-up **or has died**.
Section 5.7.3 Follow-up and Reporting of Serious Adverse	Any new SAEs reported by the subject to the investigator **that occur after the last scheduled contact,** and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported	Any new SAEs **or IREs** reported to the investigator **which** occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported

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Location	Old Text	Updated Text
Events Occurring after Last Scheduled Contact	to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow SAEs identified after the last scheduled contact until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor up to the point the event has been resolved or stabilized.	to the sponsor. This may include SAEs **or IREs** that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs **or IREs** identified after the **defined trial period and** continue to report any significant follow-up information to the sponsor **until** the event**s are** resolved or stabilized**, or the subject is lost to follow-up or has died**.
Section 15 References	15: Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Life Events Checklist for DSM-5 (LEC-5). White River Junction, VT: National Center for PTSD; 2013.	15: Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Life Events Checklist for DSM-5 (LEC-5) **- extended**. National Center for PTSD; 2013.

ADDITIONAL RISK TO THE SUBJECT:
There is no additional risk to the subjects.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-34712, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where OPC-34712 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

Otsuka Pharmaceutical Development & Commercialization, Inc.
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OPC-34712

SIGNATURE PAGE

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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

Revised CLINICAL PROTOCOL ADDENDUM for TRIAL 331-201-00061

A Phase 2, Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial of Brexpiprazole (1 - 3 mg/day) as Monotherapy or as Combination Therapy in the Treatment of Adults with Post-traumatic Stress Disorder

Protocol No. 331-201-00061
IND No. 117,549

CONFIDENTIAL – PROPRIETARY INFORMATION

Drug Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	INC Research Pharmacovigilance & Drug Safety Fax: [redacted]
Issue Date:	29 Sep 2016
Date of Amendment 1	8 Jun 2017
Version No.:	2.0

BLINDING & CONFIDENTIALITY

This addendum is a separate entity from the associated clinical protocol for Trial 331-201-00061 and provides the details of procedures and statistical methods that are blinded in the protocol, namely, the UNBLINDED randomization timing and description of certain aspects of the trial design. This document is intended for use only by Otsuka personnel or their designated agents or for review only by Institutional Review Boards, Independent Ethics Committees, regulatory authorities, or any other entity considered suitable by Otsuka. The information contained herein is unblinded and confidential; therefore, it must **NOT** be shared with or communicated to any individual at an investigational site without written authorization from Otsuka Pharmaceutical Development & Commercialization, Inc.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
IMP	Investigational medicinal product
MMRM	Mixed-effect model repeated measure
OC	Observed-case
PTSD	Post-traumatic stress disorder
QTcF	QT interval as corrected by Fridericia's formula
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SD	Standard deviation
TEAE	Treatment-emergent adverse event

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1 Background

[redacted] This protocol addendum describes the blinded aspects of Trial 331-201-00061, including a detailed description of each trial phase.

This addendum does not repeat the details of the trial design found in the protocol and should be read in conjunction with the protocol.

2 Objectives

The objective of the addendum is to present the blinded procedures from the main protocol, namely, the unblinded trial phase descriptions, timing of randomization, and the timing of the final efficacy assessments.

3 Trial Design

3.1 Blinded Design of Trial

This is a phase 2, randomized, double-blind, placebo- and active-controlled, 4-arm trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (1 - 3 mg/day) as monotherapy or as combination therapy with Zoloft (sertraline) in adult subjects with post-traumatic stress disorder (PTSD). See Figure 3.1-1 for a schematic of the trial design.

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Figure 3.1-1 Unblinded Trial Design Schematic

3.1.1 Screening

This phase is not blinded and is discussed in the full protocol.

[redacted]

3.1.3 Blinded Phase B - Treatment Phase

At Week 1, subjects will be randomly assigned in a 1:1:1:1 ratio to one of the double-blind treatment regimens.

3.1.4 End of Week 12/Early Termination

This visit is not blinded and is discussed in the full protocol.

3.1.5 Post-treatment Follow-up Period

This period is not blinded and is discussed in the full protocol.

3.2 Trial Treatments

All subjects receive daily: one tablet (active or placebo-matched brexpiprazole) and two Zoloft (sertraline) capsules (active or placebo-matched).

3.2.1 Trial Treatment Administration

Treatment administration information is not blinded and is discussed in the full protocol.

3.2.2 Brexpiprazole Administration

[redacted] Dose decreases can occur at scheduled or unscheduled visits, but dose increases can occur only at scheduled visits. No dose decreases are allowed after the Week 6 visit and no dose increases are allowed after the Week 4 visit.

[redacted]

3.2.3 Combination of Brexpiprazole plus Zoloft (Sertraline)

[redacted]

Dose decreases can occur at scheduled or unscheduled visits, but dose increases can occur only at scheduled visits. No dose decreases are allowed after the Week 6 visit and no dose increases are allowed after the Week 4 visit.

[redacted]

[redacted]

3.2.4 Zoloft (Sertraline) Administration

[redacted] Dose decreases can occur at scheduled or unscheduled visits, but dose increases can occur only at scheduled visits. No dose decreases are allowed after the Week 6 visit and no dose increases are allowed after the Week 4 visit.

[redacted]

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3.2.5 Placebo Administration

As shown in Table 3.2.5-1, subjects assigned to placebo for both treatments (sertraline and brexpiprazole).

[redacted]

4 Statistical Analysis

4.1 Sample Size

The primary efficacy endpoint is defined as change from baseline (Week 1 visit) [redacted] in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score.

Sixty-eight subjects per arm will provide at least 80% power at a 2-sided alpha level of 0.05 to detect the treatment difference of −6.5 points in primary efficacy endpoint for active arm vs placebo with a standard deviation (SD) of 13. Adjusting for 10% non-evaluable subjects, the total number of subjects to be randomized is 75 per treatment arm.

Further adjusting for 10% dropout between Baseline (Day 0) Visit and randomization, approximately 332 subjects are expected to be enrolled in the trial.

4.2 Datasets for Analysis

The following samples are defined for this trial:

- Enrolled Sample - all subjects enrolled in Placebo Lead-In Phase
- Randomized Sample - all subjects randomized into this trial
- Safety Sample - all subjects in the randomized sample who were administered at least one dose of double-blind investigational medicinal product (IMP)

- Intent to Treat Sample - all subjects in the Randomized Sample who took at least one dose of double-blind IMP and have a baseline and at least one post baseline evaluation for the CAPS-5 total score

In general, baseline of an efficacy endpoint is defined as the last available measurement before the first dose of double-blind IMP.

4.3 Handling of Missing Data

In general, missing data will be handled by analysis of mixed-effect model repeated measures (MMRM) methodology based on observed-case (OC) data from protocol-specified visits under the assumption of missing at random.

The OC dataset consists of actual observations recorded at each visit during the double-blind treatment period and no missing data will be imputed.

4.4 Primary and Secondary Endpoint Analyses

4.4.1 Primary Endpoint Analysis

The change from baseline in CAPS-5 total score will be analyzed using an MMRM methodology with unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, type of trauma, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CAPS-5 total score by visit week as a covariate. All scheduled visits during double-blind treatment will be included in the model but primary comparison will be performed [redacted].

In case the prespecified primary efficacy model does not converge, the algorithm to deal with convergence issues will be prespecified in the Statistical Analysis Plan (SAP).

The following 3 comparisons [redacted] after randomization will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED.

1) Brexpiprazole plus Sertraline vs Placebo
2) Brexpiprazole vs Placebo
3) Brexpiprazole plus Sertraline vs Sertraline

To protect the experiment-wise 2-sided alpha level at 0.05 when making 3 comparisons specified above, the statistical testing will be carried out using a hierarchical testing

procedure in the order of 1) comparison of brexpiprazole + sertraline vs placebo; 2) comparison of brexpiprazole vs placebo; and 3) comparison of brexpiprazole + sertraline vs sertraline. Additional test(s) might be added, and the order of the tests are subject to change. The final order of the hierarchical statistical testing procedure will be specified in the SAP.

4.4.2 Other Efficacy Endpoint Analysis

The following additional subgroup analysis for the change from baseline in CAPS-5 total score will also be performed:

- The Placebo non-responders subgroup analysis based on the response observed during placebo lead-in period (defined as at least 20%, 25%, and 30% change from baseline)
- The subgroup analysis based on the type of trauma (combat related Yes/No)
- The subgroup analysis by presence of psychosocial support at baseline
- The subgroup analysis by previous pharmacological treatment intervention for PTSD

Other efficacy variables are as follows:

- Change from baseline in PTSD behavior cluster sub scores of CAPS-5:[1]
  - re-experiencing cluster sub score
  - avoidance cluster sub score
  - negative cognitions and mood cluster sub score
  - arousal cluster sub score
- Change from baseline in Clinical Global Impression - Severity score
- Response at each visit as defined by:
  - decrease from baseline ≥ 30% in CAPS-5 total score
  - decrease from baseline by > 11 points in CAPS-5 total score
- Shift in CAPS-5 PTSD severity category (moderate, severe or extreme at baseline to asymptomatic, mild, moderate, severe or extreme at each visit)
- Change from baseline in Symptoms of Trauma Scale score
- Change from baseline in Hospital Anxiety and Depression Scale score
- Sleep related endpoints

The continuous efficacy endpoints will be analyzed using MMRM model similar to that of prespecified for change from baseline in CAPS-5 total score, correcting for the relevant values at randomization.

The response in variables will be analyzed at each visit using a logistic regression model including treatment as a fixed factor and baseline of the analyzed variable at randomization as covariate. Missing values will be imputed with last-observation-carried-forward approach.

Further details for each of the additional efficacy analysis and sleep endpoints will be prespecified in the SAP.

4.5 Analysis of Demographic and Baseline Characteristics

Demographic characteristics and disease severity at baseline will be summarized by descriptive statistics, eg, proportion, mean, median, SD, and minimum and maximum values.

4.6 Safety Analysis

Standard safety variables to be analyzed include adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]) and extrapyramidal symptoms (eg, the Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Scale [BARS]). Safety analysis will be conducted based on the Safety Sample defined in Section 4.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of double-blind IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.

4.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized by treatment group:

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs potentially causally related to the IMP

- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

4.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements and prolactin concentrations will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined in the SAP criteria for laboratory tests will be summarized.

4.6.3 Physical Examination and Vital Signs Data

Physical examination findings will be listed by subject.

Summary statistics for change from baseline in vital signs, body weight, and waist circumference will be provided.

Potentially clinically relevant results in vital signs and body weight will also be summarized.

4.6.4 Electrocardiogram Data

Mean change from baseline will be summarized by treatment group and by visit.

Incidence of potentially clinically relevant changes will be calculated for ECG parameters and summarized by treatment group and by visit.

For the analysis of QT and QTc data from three consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula:

$QTcB=QT/(RR)^{0.5}$, and

2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$

3) QTcN is the length of the QT interval corrected for heart rate by the Food and Drug Administration Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

Results will be summarized by visit.

4.6.5 Other Safety Data

Change from baseline in scores for the extrapyramidal symptoms (eg, the SAS, the AIMS, and the BARS) and suicidality (eg, C-SSRS) will be summarized by treatment group based on the OC dataset of the Safety Sample. Details will be described in SAP.

5 References

[1] Friedman MJ, Resick PA, Bryant RA, Brewin CR. Considering PTSD for DSM-5. Depress Anxiety. 2011;28:750-69.

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Appendix 1 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 8 Jun 2017

PURPOSE:

The sponsor has determined the need for a formal amendment to the protocol addendum approved on 29 Sep 2016 to better clarify the statistical procedures of the study in Section 4.4.1, Section 4.2, and Section 4.6.

BACKGROUND:

This amendment to the protocol addendum was introduced to:

- Change on the analyses population: to specify that the Safety Sample is a subset of the Randomized Sample, and clarify the start dose of IMP used in the definition of the Safety Sample and the Intent to treat Sample in Section 4.2.
- Change in primary efficacy analyses: to allow flexibility to change the order or add tests to the testing sequence in Section 4.4.1.
- Change in safety analyses: to clarify the start dose of IMP in baseline definition in Section 4.6.

MODIFICATION TO PROTOCOL:

Sectional Revision:

Location	Old Text	Updated Text
Section 4.2 Datasets for Analysis	The following samples are defined for this trial: • Enrolled Sample - all subjects enrolled in Placebo Lead-In Phase • Randomized Sample - all subjects randomized into this trial • Safety Sample - all subjects who were administered at least one dose of investigational medicinal product (IMP) • Intent to Treat Sample - all subjects in the Randomized Sample who took at least one dose of IMP and have a baseline and at least one post baseline evaluation for the CAPS-5 total score In general, baseline of an efficacy endpoint is defined as the last available measurement	The following samples are defined for this trial: • Enrolled Sample - all subjects enrolled in Placebo Lead-In Phase • Randomized Sample - all subjects randomized into this trial • Safety Sample - all subjects **in the randomized sample** who were administered at least one dose of **double-blind** investigational medicinal product (IMP) • Intent to Treat Sample - all subjects in the Randomized Sample who took at least one dose of **double-blind** IMP and have a baseline and at least one post baseline evaluation for the CAPS-5 total score In general, baseline of an efficacy endpoint

Location	Old Text	Updated Text
	before the first dose of double-blind IMP.	is defined as the last available measurement before the first dose of double-blind IMP**.**
Section 4.4.1 Primary Endpoint Analysis	The change from baseline in CAPS-5 total score will be analyzed using an MMRM methodology with unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, type of trauma, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CAPS-5 total score by visit week as a covariate. All scheduled visits during double-blind treatment will be included in the model but primary comparison will be performed [redacted]. In case the prespecified primary efficacy model does not converge, the algorithm to deal with convergence issues will be prespecified in the Statistical Analysis Plan (SAP). The following 3 comparisons [redacted] after randomization will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED. 1) Brexpiprazole plus Sertraline vs Placebo 2) Brexpiprazole vs Placebo 3) Brexpiprazole plus Sertraline vs Sertraline To protect the experiment-wise 2-sided alpha level at 0.05 when making 3 comparisons specified above, the statistical testing will be carried out using a hierarchical testing procedure in the order of 1) comparison of brexpiprazole + sertraline vs placebo; 2) comparison of brexpiprazole vs placebo; and 3) comparison of brexpiprazole + sertraline vs sertraline.	The change from baseline in CAPS-5 total score will be analyzed using an MMRM methodology with unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, type of trauma, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CAPS-5 total score by visit week as a covariate. All scheduled visits during double-blind treatment will be included in the model but primary comparison will be performed [redacted]. In case the prespecified primary efficacy model does not converge, the algorithm to deal with convergence issues will be prespecified in the Statistical Analysis Plan (SAP). The following 3 comparisons [redacted] after randomization will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED. 1) Brexpiprazole plus Sertraline vs Placebo 2) Brexpiprazole vs Placebo 3) Brexpiprazole plus Sertraline vs Sertraline To protect the experiment-wise 2-sided alpha level at 0.05 when making 3 comparisons specified above, the statistical testing will be carried out using a hierarchical testing procedure in the order of 1) comparison of brexpiprazole + sertraline vs placebo; 2) comparison of brexpiprazole vs placebo; and 3) comparison of brexpiprazole + sertraline vs sertraline. **Additional test(s) might be added, and the order of the tests are subject to change. The final order of the**

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Location	Old Text	Updated Text
		hierarchical statistical testing procedure will be specified in the SAP.
Section 4.6 Safety Analysis	Standard safety variables to be analyzed include adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]) and extrapyramidal symptoms (eg, the Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Scale [BARS]). Safety analysis will be conducted based on the Safety Sample defined in Section 4.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.	Standard safety variables to be analyzed include adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]) and extrapyramidal symptoms (eg, the Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Scale [BARS]). Safety analysis will be conducted based on the Safety Sample defined in Section 4.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of **double-blind** IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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