

INVESTIGATOR AGREEMENT AND EXTERNAL PROTOCOL SIGNATURE PAGE

I have read the protocol titled:

"Exploring Mechanisms of Action of \pm 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy for Posttraumatic Stress Disorder (PTSD)," MP-8 S1, Original Protocol, Version 1, November 22, 2013

I have been adequately informed about the investigational product to date. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.

I will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. I will maintain a list of sub-investigators and other appropriate qualified persons to whom I have delegated significant trial-related duties.

I will not enroll the first subject in the study until I have received approval from the appropriate EC, and until all legal requirements in my country have been fulfilled.

By signing this signature sheet I agree:

- to conduct this clinical study in compliance with ICH GCP, with the applicable regulatory requirement(s), and with the study protocol agreed to by the sponsor and given approval/favorable opinion by the EC or IRB
- to comply with procedures for data recording/reporting
- to permit monitoring, auditing, inspection and EC or IRB review
- to retain the study related essential documents according to legal requirements and as agreed with the sponsor

Clinical Investigator


.....
[Investigator's Signature]

25 Nov 2013
.....
[Date]

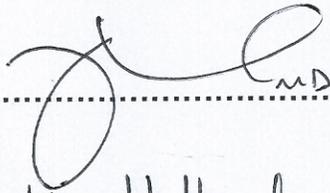
MICHAEL MITHOEFER MD
.....
[Print Name]

SPONSOR AGREEMENT

The study protocol MP8-S1 Original Protocol Version 1 was subject to review and has been internally approved by the clinical study team. The information it contains is consistent with:

- The current version of the Investigator's Brochure
- The moral, ethical and scientific principles governing clinical research as set out in the Good Clinical Practice guidelines

The investigator will be supplied with details of any significant or new findings, including adverse events.

MAPS**Signatory or Medical Monitor**.....
[Signature].....
[Date]

11/22/13

.....
[Print Name]

Julie Holland, MD

PROTOCOL MP8-S1

Original: November 22, 2013

Exploring Mechanisms of Action of \pm 3,4-methylenedioxymethamphetamine (MDMA)- Assisted Psychotherapy for Posttraumatic Stress Disorder (PTSD)

A Sub- Study of MP-8

*A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in
Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers
with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)*

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
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Medical Monitor: Julie Holland MD

1.0 Background

This investigation of physiological correlates and characterization of the psychotherapeutic processes is a sub-study conducted in subjects enrolled in the MP-8 protocol, “A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)”(IRB tracking # MAP3-10-051).

PTSD is a complex psychiatric disease characterized by a deficit in fear extinction, hyperarousal, emotional numbing, and intrusive symptoms that cause the patient to persistently re-experience a traumatic event over a period longer than a month. Existing PTSD treatments include selective serotonin reuptake inhibitors sertraline and paroxetine as pharmacologic treatments or empirically supported psychotherapeutic treatments including Cognitive Processing Therapy, Prolonged Exposure, Eye Movement Desensitization and Reprocessing, and Psychodynamic Therapy [1]. The therapies are aimed at decreasing the intensity of symptoms. However these symptoms, and specifically the intense fear associated with the traumatic memory, may themselves be obstacles to successful psychotherapy with existing treatments because patients may be unwilling to revisit traumatic memories, or if they do so the therapeutic effect may be blocked by emotional numbing or emotional flooding [1, 2].

While PTSD is considered to be treatable, it is often co-morbid with depression and anxiety, and approximately a third of the population is refractory to established PTSD drug and therapy treatments, demonstrating the continuing need for innovative treatments for PTSD [3-5]. The sponsor is currently involved in Phase 2 clinical trials of 3,4 –methylenedioxymethamphetamine

(MDMA)-assisted psychotherapy to treat chronic, treatment-resistant PTSD. MDMA-assisted psychotherapy is an innovative experimental mode of treatment that combines psychotherapeutic techniques with the administration of MDMA. It may amplify certain aspects of psychotherapy, as the pharmacological action of MDMA is thought to act as an adjunct to psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [6, 7]. Published results of the first two Phase 2 clinical trials testing MDMA-assisted psychotherapy for safety and efficacy in the treatment of chronic, treatment-resistant PTSD suggest that this approach is promising for reducing or resolving PTSD and can lead to durable improvements in PTSD symptoms [8, 9], without deleterious effects on cognition [10].

With positive results in two studies and ongoing Phase 2 clinical studies it is important to further characterize the psychotherapeutic processes that occur during treatment sessions conducted according to the manualized method used in MDMA-assisted psychotherapy. Development of self-compassion may mediate some of these psychotherapeutic processes during treatment, leading to reductions in PTSD symptoms [11]. The sponsor is interested in identifying these processes and comparing the methods with the existing process measures of other established psychotherapeutic treatments for PTSD. This will help refine the treatment method, identify which aspects of the treatment are shared across therapies and which aspects of treatment are correlated with positive clinical outcomes.

In addition to characterizing treatments correlated with positive outcome the sponsor is interested in physiological correlates of outcomes. The primary outcome measure of the Phase 2 clinical studies is the Clinician-administered PTSD Scale (CAPS), which is an established, “gold-standard” measure of PTSD symptoms, but it relies heavily on self-reported responses to interviewer questions, in addition to clinical judgment of the interviewer. Changes in physiological status or brain activity that are associated with improvement or recovery in people with PTSD may offer a means of assessing treatment response that relies less on self-report. This may be particularly important in studies with MDMA-assisted psychotherapy where blinding is difficult due to the psychoactive nature of the investigational product. Assessing beliefs concerning condition assignment found that subjects and investigators were able to guess condition assignment correctly in the first inactive placebo-controlled study of MDMA-assisted psychotherapy [10], it may be desirable to assess physiological correlates not subject to the effects of self-reported symptoms.

To support the clinical outcomes measured by CAPS from the MP-8 study, the sponsor is interested in correlations of outcomes with treatment-related changes in potential biological markers of PTSD, measured by HRV and fMRI. PTSD patients live in persistent fear of traumatic memories. The neurobiology of PTSD has been extensively studied, and, while much remains to be learned, current views in the field agree that decreased hippocampal and medial prefrontal cortex signaling resulting in increased amygdala activity, combined with predictive factors such as smaller hippocampal volume, may contribute to PTSD symptoms such as intrusive memories and hyperarousal [2]. In healthy volunteers, use of MDMA has been linked to transient changes in prospective memory and decreased left amygdala activity, which controls fearful associations with memories [12-14]. These same areas of the brain are relevant in PTSD research where increased amygdala activity is seen when compared with controls. The current MP-8 study of MDMA-assisted psychotherapy for PTSD provides an opportunity to use fMRI in a sub-group of subjects at baseline and again after treatment with MDMA to see if the same

changes seen in healthy volunteers can be measured in people with PTSD. In this way brain activity in the amygdala and hippocampus may serve as a potential indicator of response to therapy for PTSD.

2.0 Introduction

This exploratory sub-study will identify psychotherapeutic processes occurring during MDMA-assisted psychotherapy and assess the feasibility of exploring physiological correlates of clinical outcomes in subjects enrolled in the ongoing clinical trial of MDMA-assisted psychotherapy, MP-8. The sub-study will be conducted in collaboration with researchers at the Medical University of South Carolina (MUSC), Smith College and the New School for Social Research.

This sub-study will obtain estimates of effect size of physiological correlates based on response to three active dose experimental sessions, in order to properly power subsequent investigations. The sub-study will also explore correlations of clinical outcomes from the MP-8 study with treatment-related changes measured by HRV and fMRI during exposure to a personalized trauma script at baseline, one month after receiving two blinded experimental sessions in low or medium dose subjects, and two months after the final experimental session. The imaging results of this sub-study will be compared to an ongoing study of physiological correlates of Prolonged Exposure therapy with and without repeated Transcranial Magnetic Stimulation that is currently being conducted by collaborators working in association with the Veterans Affairs Medical Center in Charleston, South Carolina.

The sub-study also seeks to identify the psychotherapeutic processes that occur during psychotherapy sessions conducted according to the manualized method used in MDMA-assisted psychotherapy using a standard clinical measure to allow for comparisons to empirically supported treatments for PTSD. An additional process measure of self-compassion will be used to determine whether this may mediate treatment outcomes. MDMA-assisted psychotherapy is thought to include psychotherapy processes such as anxiety management, stress inoculation training, imaginal exposure, cognitive restructuring, focus on transference and countertransference, working with the multiplicity of the psyche, and somatic manifestations of trauma [15]. The results from this study may identify new effective therapeutic processes in MDMA-assisted psychotherapy, highlight effective processes currently used in empirically supported treatments that are shared with MDMA-assisted psychotherapy, and help refine the psychotherapeutic processes used in this treatment by identifying which aspects of the treatment are correlated with positive outcomes and which may be irrelevant or even negatively correlated with outcomes.

The identification of biological and psychological processes that are associated with MDMA-assisted psychotherapy will allow for the correlation of these psychological and physiological processes with outcomes observed in clinical trials of MDMA-assisted psychotherapy. This will make it possible to identify effective processes in MDMA-assisted psychotherapy that are similar to or distinct from conventional PTSD treatments. This knowledge will contribute to the optimization and further development of an evidence base for MDMA-assisted psychotherapy, add to knowledge about physiological correlates to PTSD and PTSD treatment, and facilitate the training of investigators who wish to conduct additional studies of this investigational treatment.

3.0 Protocol Objectives

1. To explore physiological correlates of PTSD (HRV, fMRI) measured during exposure to personalized trauma cues at baseline and two months after the final experimental session in MP-8 sub-study subjects to inform future correlations with clinical outcomes of MDMA-assisted psychotherapy measured by CAPS.
2. To explore physiological correlates of PTSD (HRV, fMRI) measured during exposure to personalized trauma cues at the primary endpoint in low or medium dose subjects and two months after the final experimental session in Stage 2 of MP-8 sub-study subjects to inform future correlations with clinical outcomes of MDMA-assisted psychotherapy measured by CAPS.
3. To explore psychotherapeutic processes observed in preparatory, integrative and experimental sessions of MDMA-assisted psychotherapy in MP-8 as predictors of clinical outcomes measured by the CAPS.
4. To explore changes in self-compassion from baseline to two months after the final experimental session in Stage 1 or Stage 2 of MP-8 sub-study subjects to inform future correlations with clinical outcomes of MDMA-assisted psychotherapy measured by CAPS.

4.0 Protocol Measures

4.1 Physiological Correlates

HRV and fMRI: Possible biological correlates of response to treatment in PTSD include HRV, the degree of change in heart rate over a given interval, and changes in brain activity in response to stressful or threatening stimuli in the form of a personalized trauma script. Examinations of HRV in people with PTSD or reporting traumas indicate that PTSD may be associated with changes in HRV, which may serve as a biological indicator of hyperarousal or dissociation [16-20]. Brain activity in the amygdala and hippocampus may also serve as a potential indicator of response to therapy for PTSD [21, 22]. Conclusions concerning the efficacy of MDMA-assisted therapy may be further supported if changes in PTSD symptoms are accompanied by changes in HRV and brain activity.

4.2 Psychological Processes

Psychotherapy Process Q-Set (PQS): The method used to evaluate psychotherapy process will be the PQS, which was first published over 25 years ago by Enrico Jones (1985). The PQS manual has since been updated and published in Jones' book *Therapeutic Action* [23]. The PQS was designed to describe psychotherapy process independent of the theoretical orientation of the practitioner. Therapeutic methods that have been examined using the PQS include: Psychoanalysis, Psychodynamic Psychotherapy, Cognitive-Behavioral Therapy, Interpersonal therapy, Interpersonal Psychotherapy, Control-Mastery Therapy, Prolonged Exposure, and Stress Inoculation Therapy [24-27]. The PQS has been used in studies of various kinds including a large randomized controlled trial for the NIMH Treatment for Depression Collaborative Research Program [28], as well as a single longitudinal case study [26].

The PQS consists of 100 items describing therapist behaviors ($n = 41$), patient behaviors ($n = 40$), and therapist-patient interactions ($n = 19$). After viewing a single session of therapy, independent raters sort the 100 items into nine categories representing items ranging from least characteristic (9) to most characteristic of the session (1). The distribution of these cards into the nine categories is set, allowing for a forced normal distribution, which counterbalances different types of observer bias. The PQS has demonstrated reliability across various treatment types [24-27], with inter-rater reliability across all items yielding alpha coefficients between 0.83 and 0.89 per rater pair, and reliability for individual items ranging between 0.50 to 0.95 [29]. The PQS has demonstrated construct and discriminant validity by successfully identifying differences between Rational-Emotive and Gestalt Therapy, Rational-Emotive and Client Centered Therapy, Psychodynamic and Cognitive-Behavioral Therapy [30]. In previous studies, the number of therapy sessions analyzed per patient has varied from a single representative session at the middle of treatment [31], to a session at the beginning and end of treatment [28], to the analysis of three sessions selected from throughout the treatment [32]. In a long-term single case study [26], every 4th session ($N = 53$) of a treatment that lasted 2.5 years was analyzed. This flexibility allows the use of the PQS to be tailored to brief treatment interventions and long-term therapy.

The Self-Compassion Scale (SCS) is a 26-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion [33]. Respondents complete the SCS by indicating how typical of them each item is along a five-point Likert scale, where 1 = "Almost never" typical and 5 = "almost always." It is estimated to take between four to eight minutes to complete. The scale has six sub-scales, Self-Kindness, Self-Judgment, Common Humanity, Isolation, Mindfulness and Over-Identified. The mean of subscale scores serves as a total score. Analysis of SCS response indicates that subscales are all related to a higher order factor of self-compassion, and the measure has high test-test reliability, at a level of 0.93. Neff reported an inverse relationship between SCS total scores and scores on measures of depression and anxiety. Self-compassion and global self-esteem are both related to positive mood and optimism, but self-compassion may be more strongly associated with stable mood and less associated with self-rumination and anger [34]. The measure will be administered at baseline and the 2-month follow-up at the end of Stage 1 or Stage 2.

5.0 Investigational Product

No investigational product will be administered in the sub-study.

6.0 Recruitment and Subject Population

Subjects will be a subset of subjects enrolled in MP-8, all remaining subjects who enroll in the ongoing MAPS-sponsored MP-8 study will be given information about the evaluation of physiological correlates and self-compassion in the sub-study. If they are interested in participating in the procedures, then the sub-study informed consent process will be completed and they will be evaluated for inclusion/exclusion criteria specific to the sub-study.

All subjects in MP8 have already agreed to analysis of video data of study visits and will be included in the PQS to evaluate the psychotherapy process.

6.1 Inclusion Criteria

Subjects eligible for participation in this study are individuals who:

1. Are enrolled in the parent study, MP-8 “A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD).”

6.2 Exclusion Criteria

Subjects cannot take part in measurement of physiological correlates if they:

1. Have a mass brain lesion
2. Have metal in their skulls, or if they have brain or heart pacemakers
3. History of major head trauma
4. Have past or present panic or extreme discomfort with being in small enclosed spaces (claustrophobia)

7.0 Planned Duration of Study

Up to 10 subjects who remain to be enrolled in the MP-8 study may qualify for participation in the physiological correlate analysis in the sub-study. MP-8 participation is anticipated to last 5-8 months depending on condition assignment, and all sub-study visits will be conducted in the same time frame. Clinical outcome assessments with the CAPS in MP-8 are completed one month after the second experimental session and 2 months after the final experimental session for Stage 1 and Stage 2. To avoid confounding primary results of the MP-8 study, assessments for the sub-study will be conducted after each clinical outcome assessment in MP-8 (see Table 1).

Process measures requiring video review will not be conducted on the same timeline as study procedures, and will be conducted post hoc, as video data becomes available.

The active sub-study visits are anticipated to last approximately 18 months from enrollment of the first subject and end at the same time the main study MP-8 study visits are complete.

Table 1. Schedule of Sub-Study Assessments

Treatment Group in MP-8 Study	Create trauma script Baseline HRV and fMRI Self-compassion Scale	Primary Endpoint HRV and fMRI	2-Month Follow-up at end of Stage 1 HRV and fMRI Self-compassion Scale	2-Month Follow-up at end of Stage 2 HRV and fMRI Self-compassion Scale
Timing in main study	During Baseline after CAPS before V1	Primary Endpoint/V13 after CAPS	End of Stage 1/ V18 after CAPS	End of Stage 2/ V33 after CAPS
Low or Medium Dose (N≤6)	✓	✓		✓
Full Dose (N≤6)	✓		✓	

8.0 Study Procedures

Subjects for the analysis of physiological correlates and assessment of self-compassion will be recruited at baseline after basic eligibility for the MP-8 study is confirmed. All available subjects enrolled in MP-8 who agree to participate in the sub-study will complete a separate informed consent process, involving review of written and verbal information on the sub-study and the neuroimaging scans. No special screening is required for the PQS as all subjects in the main study have agreed to post hoc review of video data.

8.1 Screening for Inclusion in the Measurement of Physiological Correlates

All available subjects enrolled in MP-8 who agree to participate in the physiological correlate and self-compassion analysis of the sub-study will complete a separate informed consent process, including review of written and verbal information on the sub-study.

If applicable, subjects consenting to measures of physiological correlates may need to undergo additional medical history questions or medical examinations to exclude metal in the skull.

8.2 Baseline

1. Subjects will complete the SCS.
2. Subjects will work with the Clinical Investigator to create two 6-minute long personalized scripts, one consisting of a trauma and one consisting of the subject's typical morning routine at home.
3. The subject will read each script and the investigator will record each script to audio.
4. Audio recordings will be shared with the collaborating investigators at the Center for Advanced Imaging Research (CAIR) at the Medical University of South Carolina (MUSC).
5. Audio recordings will be divided into two three minute blocks; two trauma-related blocks and two neutral blocks by collaborators at MUSC.

8.3 Neuroimaging Sessions

Subjects will participate in up to three neuroimaging visits to the CAIR at MUSC. These visits will occur at a) baseline before psychotherapy after the CAPS assessment, b) after completion of the Primary Endpoint assessment, whenever feasible, in low or medium dose subjects, and c)

after the 2-month follow-up CAPS assessment after their final experimental session.

1. Prior to each neuroimaging session, subjects complete an anatomical scan to screen for presence of metal in the body.
2. The neuroimaging session will consist of neutral and trauma blocks. During the fMRI scan, subjects will see a visual display that reads “allow” and will be instructed to allow themselves to experience the scripts. Subjects will listen to the trauma and neutral scripts while in the scanner and regions of interest will be imaged.
3. Concurrently during the scan, pulse measurements built into the fMRI scanner will be recorded during exposure to the neutral and trauma blocks.
4. The fMRI scan will be followed by a Diffusion Tensor Imaging (DTI) scan.
5. Total scan time is anticipated to be less than 40 minutes per neuroimaging session, with actual time lasting up to 50 minutes, including set-up time.
6. After the scanning session, pulse measurements will be extracted as a digital data file from which HRV will be calculated. Results of the fMRI scans and HRV will be stored and analyzed by the CAIR at MUSC.

8.4 Two-Month Follow-up After MDMA-assisted Psychotherapy

1. Two months after the final experimental session in Stage 1 or Stage 2, depending on the condition assignment of the subjects in the main MP-8 study, subjects will complete the SCS during the visit with the therapists.

8.5 Analyses of Psychotherapeutic Processes in MDMA-assisted Psychotherapy

As the ongoing MP-8 study informed consent currently allows for post hoc analysis of videos for researchers to identify principles of MDMA-assisted psychotherapy, videos from subjects included in this analysis will not require a separate informed consent form. After video recordings of MDMA-assisted psychotherapy sessions are generated from the MP-8 study, a qualified group of observers, composed of expert psychology researchers and students from a clinical psychology graduate program at the New School for Social Research, will conduct evaluations of video-recorded sessions of MDMA-assisted psychotherapy using the PQS. The members of this group will be trained in using the PQS before analysis of the video material. At a minimum, three therapy sessions, reflecting the beginning (first preparatory session), middle (drug-assisted experimental session), and end of treatment (second integration after final experimental session) will be analyzed per subject. If resources allow, up to three preparatory sessions, three to five experimental sessions, and up to fifteen integrative sessions may be analyzed per subject.

9.0 Removal of Subjects from the Study

Subjects can withdraw consent for the sub-study at any time without prejudice and it will not affect participation in the parent study MP-8 unless consent is also withdrawn for MP-8. The investigator can withdraw a subject from the sub-study, if in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of the sub-study protocol that are critical for safety or necessary for the scientific integrity of the study. If the investigator withdraws a subject from the study, the investigators will explain the reason for withdrawing the subject. If a subject is withdrawn from the parent study MP-8 they may also be required to withdraw from the sub-study.

10.0 Premature Discontinuation of the Study

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this sub-study at any time. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with federal and local regulations.

11.0 Risks of Study Participation

Risks of Creating and Listening to Trauma Related Scripts

Creating and listening to trauma-related scripts involves confronting trauma-related material, and subjects may experience increased distress during the production of trauma-related scripts for the imaging measurements. Generating the script and reading it once it is created may increase anxiety, distress or PTSD symptoms. To mitigate this risk, subjects are permitted to stop generating or reading the scripted material. If after repeated breaks subjects are unable to read an entire script, they will be dropped from the sub-study without any effect on their MP-8 parent study participation.

Risks of Neuroimaging Scanning

Functional magnetic imaging scans cannot be performed on people with metal embedded in their skulls or bodies, including but not limited to metal in their skulls, metal implants, a cardiac or brain pacemaker, or old metal fragments in the eye or retina. This does not include dental fillings. A screen for presence of metal objects will occur prior to each imaging session. If any metal is detected, subjects will not undergo imaging scans.

Noise is produced by the equipment during the scanning process. There is risk of damage to one's hearing if earplugs are not used during scanning. Subjects will be provided with earplugs prior to each scanning session.

Undergoing an fMRI scan can provoke panic or distress in some individuals, especially those with a history of claustrophobia. The scanner is open at both ends but enclosed beyond those ends, and subjects are required to remain still. Subjects will have access to an emergency call button within the scanner. Activating the button will result in study staff at the CAIR center arriving immediately and removing the subject from the scanner.

Risks and Discomforts of Video Recording Analyses for Psychotherapeutic Procedures

Risks related to subject confidentiality are described in the protocol and informed consent for the parent study. Subjects may feel uncomfortable with having their sessions recorded. The recordings are a necessary component of coding psychotherapy sessions to assess the procedures involved in MDMA-assisted psychotherapy. Subjects will receive information on who will have access to any of their recordings and will have control over any presentation of recorded material beyond viewing by researchers, trainees or regulatory agencies.

12.0 Adverse Events

An Adverse Event (AE) is defined as any untoward or unfavorable medical occurrence in a clinical research study subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subjects' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

AEs will be collected for the main study; no additional adverse events are expected to occur as a result of sub-study participation.

12.1 Adverse Event Collection

No drug is administered as a part of the sub-study. AEs will be collected during the course of the main study (MP-8). AE collection will include any AEs that occur during sub-study participation.

Medical Monitor

Julie Holland, M.D.



Study Monitor

Berra Yazar-Klosinski, Ph.D.
Phone number: 831-429-6362 ext. 104
Fax number: 831-429-6370
Email: berra@maps.org

13.0 Collection of Concomitant Medication

Concomitant medication will be collected during the course of the main study.

14.0 Clinical Laboratory Assessments

The Clinical Investigator of the main study will examine laboratory assessments gathered in screening for assessing subject eligibility for the main study. No additional laboratory tests will be performed for subjects in the sub-study.

15.0 Study Monitoring, Auditing and Documentation

Investigators and the study staff of the main study will be trained on procedures of the sub-study by qualified personnel. The main clinical study site will be monitored by site visits and telephone calls to the investigator by representatives of the sponsor. The main study site will be monitored

as appropriate for the rate of enrollment in order to comply with GCP guidelines. Data from the collaborating sites will be remotely monitored to ensure validity of the study data.

The sponsor will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

During or after the clinical protocol, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

16.0 Data Analysis

This study is primarily a feasibility study that will obtain estimates of effect size comparing post-treatment outcomes to baseline using all available data from the physiological correlates (HRV, fMRI), SCS, and the PQS. Effect size for all measures will be estimated using Cohen's techniques. Effect size estimates for a within-subject analysis of three active dose experimental sessions will be obtained from a comparison of baseline to two-month follow-up data. Subjects who were randomized to the low or medium dose group will be scanned, whenever feasible, at the beginning of Stage 2 for a second baseline comparison to two-month follow-up data. Data from each imaging session will be analyzed by collaborating researchers at CAIR following the techniques and procedures appropriate for examining changes in brain activity. Results from the PQS and SCS will be explored as mediators of clinical outcomes. Descriptive statistics will be computed overall and within the dose groups for all available data from outcome measures, including minimum, maximum, average, and standard deviation. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, may be excluded from effect size estimates.

16.1 Statistical Power

Statistical power estimates were not available for this study, as this is the first prospective study of psychological processes and physiological correlates of MDMA-assisted psychotherapy. Physiological correlates will be evaluated for predictive and prognostic power.

17.0 Informed Consent

The main study Clinical Investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. Written and verbal information about the study must be given in an understandable form. In addition to the explanation of sub-study procedures, the information should include that access to original medical records and processing of coded personal information must be authorized, and will include screening for presence of metal in the body. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the sub-study and to consider participation. The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator. The investigator will provide a copy of the signed ICF to the subject, and will maintain the original in the investigator's study file. The written ICF and any other written information to be provided to subjects should be revised whenever important

new information becomes available that may be relevant to the subject's consent. Any revised written ICF, and written information should receive approval from an IRB before use.

Written consent to take part in the sub-study includes giving the investigators' permission to view the subject's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to take part in the sub-study. The communication of this information should be documented.

18.0 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of subjects in their role as research subjects. Removing identifying information from data and restricting access to researchers should prevent the dissemination of confidential data, with or without identifying information. Despite this, privacy cannot be guaranteed. Except for the Subject Contact and Inquiry log, the informed consent and the subject code list, all data will be identified only by the subject's initials on the source document and four-digit subject number. If past medical records are needed, subjects will sign forms for the release of information upon consent to permit screening for enrollment.

Copies of audio and video recordings from the main study intended for research on principles of MDMA-assisted psychotherapy will only be marked with the subject number prior to sending to qualified researchers for the PQS analysis. Full names and addresses will not appear in these recordings. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, and qualified researchers with approval from the Clinical Investigator. Researchers, other than the investigators directly involved in the protocol, with access to data will not be provided with any information that would identify subjects by name or by other means.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data by unauthorized persons. While it is possible that individuals may be identified on audiotape or video recording through means other than their names, restricting access to audio recordings or video recordings to researchers or trainees greatly reduces the risk of a breach of confidentiality.

19.0 Payment for Participation

Subjects will receive \$75 for each neuroimaging session. Subjects will have a choice to be compensated with cash, gift cards (e.g., Wal-Mart, Target) or gift vouchers.

20.0 Costs to Subjects

There will be no costs to the study subjects for any study-related procedures. The sponsor will cover all costs of study participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation and cost of all imaging scans. Charges for treatment of the subject's condition that are unrelated to the research

study or any of its procedures will continue to be billed to the health insurance provider of the subject or to the subject him or herself.

21.0 Treatment and Compensation of Study Related Injury

No drug will be administered during the sub-study, as such study-related emergencies are unlikely to happen. Treatment of a study-related emergency would first be billed to a subject's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a subject's health insurance.

22.0 Record Retention

Investigators must retain all study records required by GCP and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to GCP in the Investigator Site File (ISF). It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

23.0 References

1. Cukor J, Spitalnick J, Difede J, Rizzo A, Rothbaum BO: Emerging treatments for PTSD. *Clin Psychol Rev.* 2009 Dec;29(8):715-726.
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