PROTOCOL MT-1

IND #63-384

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MDMA Administration in a Therapeutic Setting in People Who Have Completed the MAPS Training Program for Therapists Learning to Conduct MDMA-Assisted Psychotherapy Research in Subjects with PTSD

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1.0 List of Abbreviations

AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
C	Celsius
CAPS	Clinician Administered PTSD Scale
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
DEA	Drug Enforcement Agency
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrocloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPCL	High Purity Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LSD	d-lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamine
NK	Natural Killer
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
SAE(s)	Serious Adverse Event(s)

SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

2.0 Background Information

2.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4-methylenedioxymethamine (MDMA)-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD).

Encouraging data has been obtained and submitted to the FDA from MAPS' recently completed United States (U.S.) pilot study, Protocol #63-384 (MP1). MAPS is currently sponsoring other Phase 2 studies in Switzerland and Israel, with additional Phase 2 studies planned to start in the near future in Canada and the U.S. These Phase 2 studies are laying the groundwork for Phase 3 multi-site MDMA/PTSD research studies. A key limiting factor in MAPS' drug development plan is the need to train 20–30 male/female co-therapist teams to conduct MDMA/PTSD psychotherapy research in accordance with MAPS' treatment method [1].

MAPS is developing a training program to teach potential research teams standardized techniques and procedures for MDMA-assisted psychotherapy for use in PTSD patients. As additional, optional training, this protocol (MT-1) has been designed to offer people who have completed the initial training program the opportunity to experience MDMA in a therapeutic context. The MDMA-assisted psychotherapy training session will employ techniques learned in the initial training program. Receiving MDMA under the direction of investigators will provide participants with an in-depth understanding of how to maximize the therapeutic effects of MDMA. It will also allow participants to better draw distinctions between common, self-limited side-effects of MDMA-assisted psychotherapy and those effects that require intervention.

The training session will be conducted in a therapeutic setting over a three-day period supervised by Dr. Michael Mithoefer and Annie Mithoefer, B.S.N. The day-long MDMA session will be preceded the day before by a 90-minute preparation session with both investigators and will be followed the day after by a 90-minute integrative session, also with both investigators. There will also be daily telephone contacts between the investigators and the trainee for a week after the MDMA session, for integrative purposes, as well as integrative follow-up phone calls one and two months after the MDMA session.

There is a precedent in the history of the Food and Drug Administration (FDA) for the administration of MDMA in the context of a training program. In the 1970s, in the "Training Project for Mental Health Professionals" conducted at the Maryland Psychiatric Research Center under Dr. Albert Kurland's IND for d-lysergic acid diethylamide (LSD), 108 people with pastoral and counseling jobs were permitted by the FDA to receive LSD up to three times in a therapeutic context. The purpose of the program was to help the mental health professionals to better understand the LSD experience so as to enhance their ability to work with people who discussed LSD

experiences with them. William Richards, Ph.D., a therapist who administered the LSD to many of the mental health professionals, has written a description of the program for submission to the FDA [2]. He reports in his letter that, "in those days, all clinical employees at the Maryland Psychiatric Research Center (psychiatrists, psychologists, psychiatric nurses) involved in interactions with human subjects during the period of psychedelic effects participated in a similar training program as part of their on-the-job training when they first were hired."

The MDMA session will not be offered until appropriate Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and other authorities, if applicable, will be informed of protocol amendments in accordance with local legal requirements.

The MDMA session will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines, and applicable standard operating procedures (SOPs). The session will be conducted under a protocol reviewed and approved by an IRB; the introductory, MDMA and integrative sessions will be conducted by scientifically and medically qualified persons; the benefits of the protocol are in proportion to the risks; the rights and welfare of the participants will be respected; the investigators conducting the trial do not find the hazards to outweigh the potential benefits; each participant will give written informed consent before any protocol-driven tests or evaluations are performed.

A comprehensive review of MDMA research is contained in the Investigator's Brochure supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

2.2 Protocol Purpose

The purpose of the protocol is to provide participants who have completed the sponsor-developed training program with the optional opportunity to gain first-hand experience of the effects of MDMA administered in a therapeutic setting. Participants will receive MDMA under the direction of investigators in order to provide an in-depth understanding of how to maximize the therapeutic effects of MDMA-assisted psychotherapy administered in a research setting. The MDMA experience will also allow participants to better draw distinctions between common, self-limiting side effects of MDMA-assisted psychotherapy and those effects that require intervention.

Currently, there are no training programs designed to teach MDMA-assisted psychotherapy. June May Ruse, Ph.D. and Michael Mithoefer, M.D., with the assistance of Lisa Jerome, Ph.D., Rick Doblin, Ph.D., Ann Mithoefer, B.S.N., and Elizabeth Gibson have developed a treatment manual describing the core elements, procedures and techniques of MDMA-assisted psychotherapy [1]. The treatment manual details

descriptions of methods for therapists to provide guidance and support during MDMA-assisted sessions. The sponsor is developing a training program in which trainees will be instructed through lecture, discussion and viewing of selected segments of audio and video recordings from sessions of MDMA-assisted psychotherapy research. Trainees will develop the requisite skills and techniques to perform MDMA-assisted psychotherapy research in patients with PTSD.

The purpose of this training program is to ensure that there are enough male/female teams of therapists proficient at performing the manualized treatment to act as investigators for Phase 2 and 3 studies. At least one member of the team must have appropriate credentials to conduct psychotherapy (licensed psychotherapist, psychologist, psychiatrist or other physician with experience in treating psychological problems). The other must either be a therapist, physician, nurse, social worker, or have other experience and background judged by the investigators to be appropriate for a co-therapist. Credentials will be reviewed prior to training.

MAPS' treatment method can be conducted by therapists and researchers without any prior, personal subjective experience with MDMA, and MAPS will not require therapists conducting studies to have such experiences. Nevertheless, MAPS believes that a personal experience with MDMA, in a therapeutic setting similar to that used in clinical trials, is likely to make a significant contribution to a therapist's effectiveness conducting clinical trials with MDMA.

2.3 Supporting Information

There is a precedent for the view that it is valuable for therapists to have personal experience with the specific therapeutic techniques they are being trained to employ. Various therapeutic schools have a model of psychotherapy training that requires psychotherapists in training to undergo some or all elements of psychotherapy (Mace, 2001) [3]. While currently there is controversy as to the significance and benefits of these experiences, sometimes referred to as "personal psychotherapy," specific features of using psychoactives as adjuncts to psychotherapy support such experiences [4].

The potential value placed on personal experience is consistent with the views expressed by many of the early psychedelic therapists and researchers from the 1940s to the early 1970s, who used psychedelic sessions to train therapists. At least some therapists who underwent personal therapy reported a better understanding of their patients' experience, including both the negative and positive effects of therapy. People who are unfamiliar with the effects of a given compound in a specific setting may hold inappropriate expectations or be unaware of aspects of the setting that may enhance or hinder therapeutic effects. Investigators who administered LSD in the course of psychotherapy reported that therapists who took LSD gained better insight into their patients' experiences during LSD-assisted psychotherapy and were thus better able to aid them [5, 6].

In 2007, a survey was administered in Prague, Czech Republic, in which twenty

psychotherapists who had conducted LSD psychotherapy in the 1950s and 1960s were asked whether their own personal sessions with LSD, conducted in the context of their training, were a valuable didactic experience for their professional work as psychotherapists. On a scale of 1 (strongly agree) to 9 (strongly disagree), respondents scored a mean of 1.25 [7].

Personal experience is considered beneficial by practitioners of psychotherapeutic methods such as hypnosis and psychoanalysis, and by teachers of meditation and yoga. However, in the case of present-day MDMA research, personal experience with MDMA can only be obtained legally through participation in a government-approved protocol. Some researchers currently conducting MAPS' MDMA/PTSD studies have expressed the opinion that it would enhance the treatment that they are able to provide to study participants if they were able to experience MDMA within a controlled protocol such as this one.

There is also a precedent for FDA approval of administering psychoactive compounds as part of the training process for psychotherapists. In the 1970s, in the "Training Project for Mental Health Professionals" conducted at the Maryland Psychiatric Research Center under Dr. Albert Kurland's IND for LSD, 108 people with pastoral and counseling jobs were permitted by the FDA to receive d-lysergic acid diethylamide (LSD) up to three times in a therapeutic context. The purpose of the program was to help mental health professionals to better understand the LSD experience so as to enhance their ability to work with people who discussed LSD experiences with them [2]. William Richards, Ph.D., a therapist who administered the LSD to many of the mental health professionals, has written a description of the program for submission to the FDA as background for this protocol [2]. In this letter, he reports that the training program at the Maryland Psychiatric Center for clinical employees expected to interact with participants receiving LSD included personal experience with LSD within the same setting.

Daniel Helminiak STL, Ph.D., Ph.D., LPC, a Professor of Psychology at the University of West Georgia, was one of the original participants in the "Training Project for Mental Health Professionals". Helminiak reports long-term benefits to his ability as a therapist from undergoing a supervised experience with LSD, stating in a letter written for submission to the FDA as background for this protocol, "Looking back over 35 years, I continue to see that LSD experience as a major, positive event that enhanced my abilities as a priest, therapist, educator" [8].

2.4 Previous MDMA Research

To date, MDMA has been administered to approximately 412 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of drug-related Serious Adverse Events (SAEs) [9-21].

The initial and supplemental doses of MDMA to be used in this protocol are identical to those in use in the studies of MDMA-assisted psychotherapy research completed or

currently underway in the U.S., Switzerland and Israel. Previous researchers have also used doses within this range [10, 17, 22-24].

2.5 Discussion of PTSD

PTSD is a serious, worldwide public health problem for which a wider array of effective treatments is needed. In the U.S., the lifetime prevalence of PTSD in the general population is between 6 and 10% [25]. PTSD is common in other countries as well [26-30]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [31] , and it is estimated that the number of service members returning home with PTSD will be between 75,000 and 225,000 [32]. In 2004, the U.S. Veterans Administration spent $4.3 billion on PTSD disability payments to approximately 215,000 veterans, most of them from the Vietnam War [33]. In countries where there is endemic armed conflict, the incidence of PTSD in civilians is often far greater [34-36]. PTSD is typically a chronic illness [37, 38], associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide [28, 37, 39, 40].

An array of psychotherapeutic options exists for treating PTSD and two Selective Serotonin Reuptake Inhibitors (SSRIs) (sertraline and paroxetine) are approved as PTSD treatments in the U.S. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [41, 42], and at least one study of Paxil indicated that men with PTSD did not respond to this drug [43]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

In recent years, there has been growing research into drugs or other methods that may augment the effectiveness of psychotherapy for PTSD. Examples of this are virtual reality-assisted exposure therapy [44, 45], and D-Cycloserine-assisted psychotherapy [46]. MDMA-assisted psychotherapy is another such approach that is being rigorously tested.

3.0 Protocol Objectives

Primary Objective

The primary objective of the open-label MDMA session is to support and expand the knowledge and skills of therapists trained in MDMA-assisted psychotherapy research in patients with PTSD. Those who undergo the MDMA session are expected to grasp more completely the effects of the study drug in a therapeutic setting.

Safety Objective

To monitor and assure the safety of MDMA in participants throughout the clinical protocol.

4.0 Investigational Product

4.1 MDMA Activity Related to Proposed Action

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive 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 [47, 48]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the principal investigator of this protocol reported reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy instead of placebo [49]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion [22-24, 50-54]. Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with ecstasy (see for example [22] versus [54]). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to the therapeutic effects of MDMA. It is significant that anxiety is reduced without depressing the sensorium, and that patients can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit patients to explore usually upsetting thoughts, memories or feelings. Facilitated recall and unusual and potentially innovative shifts in thinking and perception may contribute to generating new perspectives about past or current thoughts, feelings and experiences.

4.2 MDMA Description

The compound to be used in this protocol is MDMA. This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [55-57]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower.

4.3 MDMA Compounding, Doses and Labeling

This is an open-label protocol. All participants will receive an initial dose of 125 mg of MDMA followed by a optional supplemental 62.5 mg dose. MDMA bulk will be sent to the investigator for compounding by the pharmacist. MDMA will be weighed into 125 and 62.5 mg doses (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules by a pharmacist under the direct observation of the investigator who has been issued the Schedule 1 license.

The two doses, 125 mg and 62.5 mg, of MDMA will be stored in separate bottles labeled with the protocol number, drug name, lot number, dosage, the sponsor name and a statement that the drug is for clinical-trial-use only. Labels for each dose and bottle of MDMA will be provided by the sponsor and applied by the pharmacist. All packaging and labeling will all be done in the presence of the investigator.

4.4 MDMA Accountability
Forms will be provided to track drug accountability and administration throughout the study. Drug accountability will be reviewed during routine monitoring visits.

4.5 MDMA Storage and Handling
MDMA is a Schedule 1 compound and will be stored and handled in compliance with relevant Federal and State regulations. In accordance with Drug Enforcement Administration (DEA) requirements, the principal investigator will be responsible for storing and dispensing the MDMA. It will be stored in a safe mounted to the floor, that has been inspected and approved by the DEA for this purpose. Only the principal investigator with the Schedule 1 license will have the combination to the safe. The room in which the safe is mounted has an alarm system and will be locked whenever the investigator or his nurse is not present.

Investigational product will only be removed from the safe for one subject at a time at the time of the session and the MDMA will not leave the premises. MDMA will be administered orally with a glass of water. All doses administered will be recorded on the appropriate accountability logs.

Records pertaining to the use of Schedule 1 compounds will be maintained in accordance with relevant Federal and State Regulations. They will be kept separate from other records and will be maintained in a locked cabinet mounted to the wall in a locked office with an alarm system.

4.6 MDMA Stability
Complete details on the chemistry, manufacturing and control of the MDMA Hydrocloride (HCl) to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University in 1985. The identity and purity of this MDMA was confirmed using High Purity Liquid Chromatography (HPLC) in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor in relation to the study of MDMA-assisted psychotherapy in people with PTSD, the analysis found it to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February, 2006 continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9 pure.

5.0 Protocol Design
This unblinded study protocol is designed to permit up to 20 participants interested in conducting studies of MDMA-assisted psychotherapy research in subjects with PTSD to receive MDMA within a therapeutic setting. Participants can enroll in this protocol only after successfully completing the sponsor-developed MDMA/PTSD training program.

The investigators will administer a single MDMA session in their treatment facility using the same setting and dosing employed in their Phase 2 study of MDMA-assisted psychotherapy. Participants will undergo a 90-minute preparatory session with the investigators one day prior to undergoing the MDMA session. Each participant will undergo a day-long MDMA session within a psychotherapeutic context. They will receive 125 mg MDMA and a supplemental dose, if mutually agreed upon by investigators and participant, of 62.5 mg. Following the session, they will stay overnight at the study site. Each participant will have a 90-minute, integrative psychotherapy session on the day after the MDMA-assisted psychotherapy session. Undergoing a preparatory and integrative session before and after the MDMA session will serve as a means of preparing for the MDMA experience and addressing any transient distress, if any, arising from the MDMA session. Telephone calls will be made to participants each day for seven days after the MDMA session as well one and two-months after the MDMA session, as additional opportunities to help subjects understand and integrate the experience. All sessions will be recorded to audio and video, and participants will receive copies of their sessions upon request.

5.1 Planned Duration of Protocol

The duration of the active participation in the protocol will be three days of clinic visits followed by integrative telephone calls occurring daily for a week and then again 1 and 2 months following the MDMA session. The last telephone call at two months will be considered to have completed the protocol. Assuming the enrollment of 20 participants, the expected time from enrolling the first participant until the final participant completes this protocol is 2 to 3 years. This estimate is based on enrollment of approximately one participant per month, but assumes delays relating to the scheduling and completion of the training program.

5.2 Randomization and Subject Numbering

This is an open-label, single-arm protocol. Each participant will be assigned a three-digit subject number in ascending order upon enrollment at Visit 1. The first number will indicate the study site.

5.3 Recruitment and Subject Population

The investigator will recruit men and women aged 21 or older who have successfully completed the sponsor-developed training program for MDMA-assisted psychotherapy for research in PTSD patients. After written informed consent, participants will undergo further screening to confirm eligibility.

5.3.1 Inclusion Criteria

Individuals eligible to be enrolled into this protocol are participants who:

1. have successfully completed the sponsor-supported program for training therapists to perform MDMA-assisted psychotherapy research;
2. are at least 21 years old;

3. may have a history of a mood disorder (except bipolar affective disorder type I, see exclusions) and/or an anxiety disorder or other non-excluded psychiatric disorder, but may not meet criteria for any current psychiatric diagnosis not in remission;
4. are willing to commit to medication dosing\experimental session and integrative follow-up sessions, and to complete evaluation instruments;
5. are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the MDMA session to avoid the possibility of interactions (the interval will be at least 5 times the particular drug's half-life). Participants may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual);
6. agree that, for one week preceding the MDMA session will refrain from:
    a. taking any herbal supplement (except with prior approval of the research team);
    b. taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team);
    c. taking any prescription medications with the permission of their physician (with the exception of birth control pills, thyroid hormones or other medications approved by the research team);
7. agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before the experimental session;
8. refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session;
9. agree not to use caffeine or nicotine for 2 hours before and 6 hours after the dose of MDMA;
10. are willing to remain overnight at the study site;
11. agree to have transportation other than driving themselves after the integrative session on the day after the MDMA session;
12. are willing to be contacted via telephone for all necessary telephone contacts;
13. are of childbearing potential who have a negative pregnancy test and agree to use an effective form of birth control;
14. are proficient in speaking and reading English;
15. agree to have all clinic visit sessions recorded to audio and video.

5.3.2 Exclusion Criteria

Individuals not eligible to be enrolled into this protocol are those who:

15. are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control;
16. have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 or, dissociative identity disorder (with history of affective disorder or anxiety disorder permitted if currently in remission)
17. have current psychiatric diagnosis other than adjustment disorder.
18. have evidence or history of coronary artery disease or cerebral or peripheral vascular disease, hepatic disease with abnormal liver enzymes, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration;
19. have hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions [58];
20. have history of history of hyponatremia or hyperthermia;
21. weigh less than 48 kg;
22. have used "ecstasy" (material represented as containing MDMA) within 6 months of the MDMA session;
23. require ongoing concomitant therapy with a psychotropic drug;
24. meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;
25. is not able to give adequate informed consent;
26. have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.

6.0 Methods

Participants who have successfully completed the MAPS therapist training program will receive consent materials describing the protocol.

After consenting to take part in the protocol, participants will be screened by a physician who will obtain medical and psychological history by interview and perform a general physical examination, brief neurological exam and clinical laboratory assessments (see 6.2.1 for details). Further examination will be medical-history directed if the investigators have additional questions about participant eligibility. Additional tests or assessments may be requested. If, after reviewing all information, the investigators conclude that a participant is eligible they will arrange and schedule a three-day period during which the preparatory session, MDMA session and integrative session will take place. If tapering medication is necessary, the MDMA session will be scheduled to occur after washout is complete. Eligible participants will travel to the offices of the investigators, where the participant will have one, 90 minute-long preparatory session with the investigators, followed by a day-long MDMA-assisted psychotherapy session. The participant will have a 90-minute integrative session with the investigators on the

morning after the MDMA session. A week of integrative daily telephone contact, as well as integrative follow-up telephone calls one and two-months after the MDMA session will be made to participants.

As safety measures, vital signs and a measurement of psychological distress will be assessed during the MDMA session. Participants will rate their current degree of subjective distress with a single-item, self-report scale, the Subjective Units of Distress (SUD) scale, repeatedly during the MDMA session, with the degree of distress marked along seven points. Spontaneously reported side effects, Adverse Events (AEs) and SAEs will be recorded during the MDMA session and for seven days following the session. The investigators will also assess participant well-being during the introductory session, integrative session and integrative telephone calls for seven days following the MDMA session and the follow-up telephone calls 1 and 2 months after the MDMA session.

For educational purposes, the investigators will encourage participants to produce a written narrative account of the MDMA session, during Visit 3, but this is not a requirement of participation. It will not be collected since it is only for personal reflection. This is expected to take between 10 and 30 minutes. Likewise, participants may use other means of expression, as visual art, to represent their experience.

Table 1: Time and Events Table

Visit #	Pre-Study	V1	V2	V3	Phone Contact	Phone Contact
Type of Visit	Screening may take place over more than one day	Intro/Prep	MDMA Dosing	Integrative Therapy	7 days of Phone Contact	Follow up
Approximate Study Day	Up to one month prior to Visit 1	0	1	2	3 to 9	31 and 61
Visit Timing and Windows		1 day prior to MDMA Dosing	MDMA Dosing	1 day Post-Dosing	2-8 days Post-Dosing	30 and 60 days Post-Dosing
Provide Consent Materials/Informed Consent	X					
Medical History (by interview)	X					
Psychiatric History and Evaluation	X					
General Physical Exam (BP, Pulse, Temp, brief systems check)	X					
Brief Neurological Exam	X					
EKG	X					
Clinical Laboratory Tests	X					
Collect Concomitant Medication	X	X	X	X	X	X
Start Medication Taper (if applicable)	X					
Medication Taper complete (if applicable)		X				
Study Enrollment (if all Inclusion and no Exclusion met)		X				
Preparatory Session		X				
Record to Audio/Video		X	X	X		
Drug Screen			X			
Pregnancy Screen (if applicable)			X			
Administer MDMA/Therapy			X			
Blood Pressure (MDMA Session)			X			
Pulse (MDMA Session)			X			
Body temperature (MDMA Session)			X			
SUDS			X			
Overnight Stay			X			
Integrative Therapy Session				X		
Narrative Report (optional)				X		
Integrative Telephone Contact/General Well Being					X	X
Adverse Events Requiring Dr Visit			X	X	X	
Spontaneously Reported Side Effects			X	X	X	
Adverse Events that are of Concern to the Participant			X	X	X	X
Serious Adverse Events		X	X	X	X	X
Study Termination						X

6.2 Visit Descriptions

6.2.1 Prescreening and Screening

After giving written informed consent, a screening number will be assigned to each participant. The screening number will be used on all subject records prior to enrollment. Participants will provide a medical and psychological history through interview and will undergo a general physical examination performed by a physician who is not one of the investigators. The examination will involve the following procedures: blood pressure, pulse, height, weight, body temperature, examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities, brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function) , electrocardiogram (EKG), clinical laboratory assessments to include [Alanine aminotransferase (ALT/SGPT); albumin:globulin (A:G) ratio; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, total; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide; chloride, serum; creatinine, serum; globulin, total; glucose, serum; potassium, serum; protein, total, serum; sodium, serum, Complete Blood Count (CBC), which includes: Hematocrit; hemoglobin; mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); red cell distribution width (RDW); percentage and absolute differential counts; platelet count (RBC); red cell count; white blood cell count (WBC), Urinalysis, which includes: Color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen and Thyroid functions: TSH (high sensitivity), Free T4 Free T3]. In addition, Human Immunodeficiency Virus (HIV) serology will be performed. Results of HIV serology will be kept confidential, and appropriate referral for counseling will be made if necessary. The clinical laboratory values will not be captured in the Case Report Form (CRF), but will be used to establish eligibility and will be kept with the subject's source record. A urine-dip pregnancy test for females of childbearing potential will be performed as well. If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated.

The investigators will review this information and will contact the participant if all inclusion criteria and no exclusion criteria are met and will schedule the introductory session, MDMA session and integrative session to occur within a three-day period. Any participant who must refrain from taking a medication will begin tapering off that medication, with the MDMA session scheduled to occur after complete washout. The entire visit should take between 1½ and 2½ hours. This screening may take place over more than one day and up to one month prior to visit 1.

6.2.2 Preparatory Session (Visit 1)

The investigator will inquire about any possible changes in the participant's health to ensure that they continue to meet eligibility criteria and if applicable, will confirm that they have appropriately tapered off of medications. After eligibility is confirmed the participant will be considered enrolled and will be issued a subject number. The

participant will undergo a 90-minute preparatory session with the investigators at their offices the day prior to the MDMA session, in part to model the sequence of events that an individual receiving the therapy in a clinical treatment trial would experience and in part to reduce the likelihood of psychological distress during the MDMA session. The preparation session will follow the format used in current studies of MDMA-assisted psychotherapy.

The participant and investigators will discuss goals for the MDMA session and will review what will happen during the MDMA session, following standard procedures and techniques discussed in the sponsor-developed treatment manual. However, these will be adapted for the present context in which the subject does not have a psychiatric disorder, The investigators and participant will discuss the fact that it is not possible to predict the content of the MDMA session, and that specific psychological issues may arise in the course of self exploration stimulated by the MDMA. Participants will be reminded that difficult emotions, including grief, rage and fear or panic, may arise during MDMA-assisted psychotherapy sessions, and that sometimes the process can produce surprising and profound experiences even in people without any psychiatric conditions.

If a participant would like another individual present during the MDMA session, a meeting between the investigators and that individual will be scheduled during the introductory session. The introductory session will be recorded to audio and video. The investigators will supply the participant with a set of instructions and restrictions for conduct 24 hours prior to receiving MDMA, including restrictions on food and alcohol consumption. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before the MDMA session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session. Participants must not use caffeine or nicotine for 2 hours before and 6 hours after the dose of MDMA. All SAEs will be recorded from the time the participant is enrolled at Visit 1.

6.2.3 MDMA Session (Visit 2)

On the day of the MDMA session, the participant will arrive approximately one to one and a half hours prior to the MDMA session. Continuing eligibility will be confirmed and a urine drug screening and, if appropriate, a urine pregnancy test will be performed. If the subject continues to meet criteria and the participant reports that he/she followed appropriate rules and restrictions, the session will proceed; a positive pregnancy screen is cause for withdrawal from the protocol, a positive drug screen will be reviewed by the investigator and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study.

The investigators will review procedures for the MDMA session as they would for an MDMA-assisted psychotherapy research session. The investigators will record the entire session to video and audio. The session will last for eight hours or longer, followed by an overnight stay at the study site.

The investigators will follow standardized techniques and procedures for an MDMA-assisted psychotherapy research session as described in the treatment manual used for training, including familiarizing the participant with the space and equipment, and reviewing session goals and the logistics of the session. Participants will complete the SUD just prior to initial dose administration.

At approximately 10:00 A.M., participants will receive the initial dose of 125 mg MDMA along with a glass of water. The participant will sit or recline on comfortable furnishings, and there will be eyeshades and a program of music available if the participant wishes to use them. The participant will be encouraged to spend much of the time focusing attention on their inner experience without talking, but may speak to the investigators whenever they wish, and will receive guidance and support as needed. If the subject has not spoken within an hour, the investigators will inquire briefly about their experience.

Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first 6 hours of the MDMA-assisted session and every 30 minutes for another 2 hours. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic or pulse 110 are exceeded. Participant body temperature will be measured via tympanic thermometer and participants will complete the SUD every 60 minutes, until the session is over, allowing a window of plus 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the investigators can make a greater number of measurements as their clinical judgment dictates. The investigators will record any spontaneously reported side effects during the session.

A supplemental dose of 62.5 mg MDMA, which is half the initial dose, will be administered approximately 1.5 to 2.5 hours after the initial dose upon mutual agreement between the investigators and participant.

A support-individual who has previously agreed to remain with the participant during the MDMA session may arrive during the session.

The investigators will remain with the participant until the physical and psychological effects of the session have substantially subsided and the subject is judged to be in a stable condition and appears to have returned to baseline mental status. The investigators will end recording to video when they have established that the participant returned to baseline function or is very close to doing so.

The participant will remain at the study site overnight, in a comfortably furnished suite that allows for accompaniment by a significant other, friend or attendant. An attendant will remain with any participants who are unwilling or unable to locate another individual to stay with them at the study site during the overnight stay. The attendant will be of the same sex as the participant, and he or she will be trained for assisting in this protocol. Attendants will be selected for their ability to act as reliable and compassionate

attendants to participants while allowing participants room for introspection or further self-exploration as needed. All participants will receive instructions for contacting one of the investigators if needed, via telephone or 24-hour pager.

Participants will be instructed not to use caffeine or nicotine for 6 hours after the dose of MDMA. Spontaneously reported side effects, AEs of concern to the participant, and AEs requiring a doctor's visit will be collected starting on the day of the MDMA session through the seventh telephone daily telephone call. All SAEs will be recorded.

6.2.4 Integrative Session (Visit 3)

On the morning after the MDMA session, the participant will meet with both investigators during a 90-minute integrative therapy session to discuss their experience of the MDMA session. The discussion may include processing any thoughts, feelings or memories that arose during the session, addressing any goals set at the start of the session, and relating the MDMA session to anything the participant learned about MDMA-assisted psychotherapy research prior to the session, including information gleaned from the training program. Whenever possible the investigators and participant will attempt to follow the procedures for integration sessions described in the treatment manual. The integrative session will be recorded to audio and video. If the participant has generated a narrative report of their experience during the MDMA session and wishes to share it with the investigators, they may do so at this time. It will not be collected it is only for personal reflection. This is expected to take between ten and 30 minutes. Likewise, participants may use other means of expression, as visual art, to represent their experience.

The participant must have a pre-arranged ride from the study site to the place where she or he is residing, and if the participant has been unable to arrange transport, then the investigators will assist the participant in locating a ride to the location where the participant is staying.

If the participant confronted unexpectedly intense or disturbing material during the MDMA session, the investigators will provide means of continued contact throughout this day as needed. The integrative telephone contact schedule will be reviewed and additional integrative sessions with the participant may be scheduled, if needed.

Spontaneously reported side effects, AEs of concern to the participant, AEs requiring a doctor's visit and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded.

6.2.5 Daily Integrative Telephone Contact for Seven days after MDMA Session

The investigator will contact the participant daily for 7 days after the MDMA session. The integrative telephone contact will be for a brief check-in lasting 5 to 15 minutes, or as long as necessary to address any participant's concerns and to assess participant well-being. Additional telephone contact can be initiated at the request of the investigators or participant.

6.2.6 Integrative Telephone Contact 1- and 2-months post MDMA Session

The investigator will contact the participant 1 and 2 months after the MDMA session. Integrative telephone contact will be for a brief check-in lasting 5 to 15 minutes, but with duration permitted to last as long as necessary to address any participants concerns and to assess the participant's general well-being, whether their MDMA experience affected their conducting therapy and whether the experience matched their expectations.

AEs of concern to the participant and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded.

6.3 Removal of Participants from MDMA Administration

Participants can withdraw consent at any time without prejudice. The investigator can withdraw a participant if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of the MDMA session and related visits that are critical for safety. If the investigator withdraws a participant from the session, the investigators will explain the reason for withdrawing the participant.

Participants will be clinically monitored after withdrawal, the cause of which will be recorded in the participant's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE resolutions, if applicable.

6.4 Premature Discontinuation of Program

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the protocol at any time. If the protocol is prematurely terminated, the investigator will promptly inform participants and will provide appropriate follow-up to participants, if necessary. If the protocol is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. Participants will still receive recordings of sessions if they request them.

7.0 Risks In Study Participation

7.1 Screening

Medical data will be collected via medical and psychiatric history interview, general physical examination, and additional tests, assessments or interviews, if applicable. Submitting to a full medical examination and psychiatric assessment may be time-consuming, distressing or uncomfortable for some. These procedures are intended to ensure that only those without any contraindicated conditions for receiving MDMA are enrolled. Because medical history, physical examination and the collection of laboratory specimens are all part of the screening procedure, they cannot be omitted from the protocol design.

7.2 Risks and Discomforts Associated with Drawing Blood

Prior to enrollment, blood will be drawn as part of screening to assessing eligibility. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood-draw site. There is also a remote possibility of inflammation or infection at the blood-draw site.

7.3 Risks of Receiving MDMA

Side effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies in non-psychiatric populations. Common side effects include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common side effects include restlessness, parasthesias (odd somatic feelings, such as tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, and nystagmus (eye-wiggling). These effects are transient and wane as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on drug side-effects is contained in the Investigator's Brochure.

MDMA may produce mild alterations in sensory perception and altered perception of time [9, 22, 54]. Women may be more sensitive to these effects [24]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [15].

Participants may discuss emotionally distressing or embarrassing issues during their MDMA session. This may cause psychological distress.

7.3.1 Cardiovascular Effects

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 1.5 to 2.5 hours, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. Approximately 5% of participants enrolled in controlled trials with MDMA have had elevations in blood pressure above 200/100 mmHg or above a cut-off of 140/90 mmHg [54, 59]. Table 2 shows the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. No subjects in the completed trial or other clinical trials using MDMA have required any clinical interventions for elevated blood pressure, pulse or temperature, and all values returned to normal spontaneously. While maximum peak blood pressure during a given session in some cases rose above the cut-off for making more frequent measures (150 Systolic Blood Pressure (SBP) or 110 Diastolic Blood Pressure (DBP). The degree of additional blood pressure and pulse elevation after a second dose of MDMA that is half the original dose and given 1.5 to 2.5 hours after the first dose is minimal. Preliminary data gathered by Michael Mithoefer, the principal investigator who recently conducted a study of MDMA-assisted psychotherapy in 21 participants with PTSD, reports that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose.

Table 2. Physiologic Data: Increases over Baseline and Range of values

All Experimental Sessions

Highest recorded increase over baseline per experimental session	MDMA	Placebo
	Mean increase (St. Dev.) [Range of values]	Mean increase (St. Dev.) [Range of values]
Systolic blood pressure, mmHg	28.21 (14.11) [96-179]	13.38 (10.40) [83-157]
Diastolic blood pressure, mmHg	15.38 (6.85) [56-113]	10.94 (6.93) [60-102]
Heart rate, beats/minute	28.13 (11.87) [60-141]	16.69 (12.35) [68-107]
Temperature, °C	0.72 (0.52) [36.6-37.83]	0.42 (0.32) [36.39-37.76]

Group comparisons of vital signs were tested for change pre-session (15 minutes prior) to highest recorded and pre-session to post-session (6 hours post) using *t*-tests. There was a significantly greater increase in all physiologic measures from pre-session to highest recorded value during experimental sessions for the MDMA group than for the placebo group ($p < .05$). There were no significant differences when comparing changes from pre-session to post session ($p>.05$). All values returned to pre-session norms by six hours after session completion.

7.3.2 Psychological Distress

Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from investigator, with occasional use of benzodiazepines for anxiety. In the proposed protocol, participants may confront emotionally intense or upsetting memories, thoughts and feelings. Signs of psychological distress, panic or other unpleasant psychological reactions may not be as strong as expected in people with psychiatric disorders, but may still be present.

Less commonly, mild anxiety and depressed mood are reported 1–3 days after MDMA administration [23, 24], and see the IB. Some of these effects are likely to occur, but it is expected that proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects.

7.3.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body

temperature [24], and ambient temperature does not enhance or attenuate this slight elevation in humans. Maximum body temperature could rise above normal temperature, as with the maximum peak of 100° Fahrenheit (F) during the first experimental session in the sponsor's recent Phase 2 trial (n = 23, MDMA and placebo conditions combined), but body temperature returned to normal without treatment other than simply lowering the ambient temperature, which may or may not have been necessary.

7.3.4 Immunological Changes

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. A research team in Spain has studied the acute immunological effects of one or two doses of 100 mg MDMA [60-63]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunsuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings [64-66]. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [61, 67]. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose [63, 68], and a second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [68]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the first dose. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

7.3.5 Abuse Liability

MDMA is classified as a Schedule 1 compound, largely on the basis of its growing popularity at nightclubs and parties in the early to mid-1980s. The DEA placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use [69]. Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA [70-72]. However, monkeys will "pay" higher prices in lever presses for psychostimulants than they will for MDMA [73, 74]. Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence [75, 76], though studies of non-representative samples have reported higher rates of dependence [77]. Most regular ecstasy users report taking ecstasy no more often than once a week [78]. Taken together, an examination of findings in humans

and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

There is no evidence that MDMA-naïve, healthy volunteers exposed to MDMA in previous Phase 1 or Phase 2 studies have been motivated to seek out and use MDMA in non-medical settings. When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after receiving MDMA in a controlled research setting, (p. 166) [24].

In the currently proposed protocol, diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

7.3.6 Toxicity

The toxicity of MDMA has been investigated in numerous animal and in-vitro studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed [79], and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Serious MDMA toxicity is rare even in uncontrolled settings, considering the millions of users taking ecstasy of unknown identity, potency, and purity [80-82], with many users consuming estimated MDMA doses that are several times higher than those used in the proposed program, without any apparent toxicity. Under unsupervised and nonmedical conditions, the most common SAE involves hyperthermia, described in Appendix A. In addition to hyperthermic syndromes, other rare AEs include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia, and these are described in more detail in the Investigator's Brochure. The majority of ecstasy users visiting emergency departments do so because of anxiety or panic [83, 84]. In the proposed clinical protocol, volunteers will be excluded on the basis of any conditions that might increase risk of adverse events occurring and participants will be carefully monitored for signs and symptoms of these unlikely events. Contingency plans for responding to these events are described in Appendix A.

7.3.7 Potential Neurotoxicity Associated with Ecstasy Use

Extensive studies in animals indicate that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nucleus, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density [85-87], with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin [88]. Similar changes can be induced by methamphetamine and other psychostimulants [89-92]. Previous studies in nonhuman primates overestimated human-equivalent doses [93], and previous studies in

rodents may also have overestimated human-equivalent doses [94]. Studies in rodents and monkeys that employed lower or fewer doses of MDMA, or that involved self-administration, have failed to find some or all of the markers of serotonin neurotoxicity listed above [70, 95-97]. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [98]. However, they are basing their case on studies that employed inappropriately high doses of MDMA, and studies comparing the effects of repeated use of ecstasy, often along with other drugs, as discussed below.

There is controversy as to whether analogous changes in brain serotonin occur in humans, and a wealth of literature exists that compares ecstasy users to non-users [99]. Earlier studies were retrospective and possessed a number of methodological flaws, particularly in relation to appropriate matching of ecstasy users with controls. Later research employed longitudinal study designs, allowing for comparisons over time. Retrospective and longitudinal imaging studies have detected decreased estimated serotonin transporter (SERT) sites in current heavy ecstasy users when compared with controls [100-102], but with estimated SERT sites returning to normal or numbers inversely related to period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users [99, 103, 104]. A number of these studies reported impaired cognitive function only in heavy users, and not in moderate users, and some recent studies suggest that use of other drugs may contribute to impaired cognition [105-108], though other studies also reported that abstinence from ecstasy did not attenuate memory impairment in heavy users [102, 109]. There is also some evidence that ecstasy users are more likely to report symptoms of anxiety or depression, and to exhibit more behavioral impulsivity than non-ecstasy user controls [110-113]. Findings from prospective and longitudinal studies suggest that young people with existing psychological problems are more likely to try ecstasy than people without these problems [75, 76], and it appears that polydrug use may contribute to this association [110, 113-115]. Findings from retrospective studies are of limited value in estimating the potential risk of neurotoxicity from two doses of MDMA, as average cumulative dose and frequency of use in most of these studies is considerably higher than doses in human trials of MDMA. A better estimate of the potential risk of neurotoxicity can be found in findings from prospective studies comparing people before and after their first use of ecstasy.

Starting in the early 2000s, a team of researchers in the Netherlands has examined samples of people before and after reporting their first uses of ecstasy. These researchers have assessed estimated SERT sites, chemical markers of neuronal injury, changes in cerebral blood flow, performance and brain activity related to a working memory task, and cognitive function in samples of ecstasy users reporting an average use of 1 to 3 tablets [116-119]. The team also performed studies expressly in heavy ecstasy users [120-123]. They failed to find reductions in SERT sites, signs of neuronal injury or changes in performance on or brain activity during a working memory task in samples reporting use of no more than six ecstasy tablets [116, 117]. They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else, and they failed to find any markers of neuronal injury [117]. Low use of ecstasy also failed to alter brain activity or performance on a measure of working memory [116]. When comparing cognitive function in people before and after their first use an average of 3.2 tablets and non-

user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users [119]. It is notable that the study examining SERT sites and cerebral blood flow did not employ non-user controls, and that all participants in the study of cognitive function performed within the normal range, and that one individual had reportedly used ecstasy on 30 occasions rather than the limit of 10 occasions set for the other studies. Furthermore, there are some findings that at least women who decided to use ecstasy had higher impulsivity scores prior to use [124]. Taken together, their findings fail to confirm serotonergic neurotoxicity after low ecstasy use, yet found some possible indications of impaired memory.

The risks of neurotoxicity are minimal in the proposed protocol. This is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. Nevertheless, the risks of neurotoxicity arising from MDMA administration will be described and noted in application materials prior to and during the completion of the application, and the investigators will informally monitor for any signs of changes in cognition after the MDMA-assisted session.

7.3.8 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, as discussed below in the "Pharmacology" section and in the Investigator's Brochure. Pregnant and lactating women will be excluded from participation in the proposed protocol, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each client-role session and must agree to using birth control during the period of the protocol.

7.4 Medical Emergencies

The preparatory session, MDMA session and integrative session, will be conducted in the psychiatric offices of the investigators. The offices are located 2.6 miles from the nearest emergency room. The office will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. Benadryl, injectable epinephrine and other standard emergency drugs and equipment will be available on-site as a means of treating any potential allergic reactions or other medical emergencies. Available emergency medications include antihypertensive agents (such as nitroprusside and labetolol), pressor agents, anxiolytics, and intravenous fluids. In addition to drugs, the crash cart will contain a defibrillator (with rhythm monitoring capability), an oxygen tank, a 12-lead electrocardiogram (EKG) device, a suction device, a pulse oxometer, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). Equipment for placing an arterial line and monitoring arterial pressure will be present. For a recently completed Phase 2 trial, the researchers have established (in communication with the FDA) contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of case reports of toxicity in illicit MDMA users reported by Baggott and colleagues in 2001 and in the current Investigator's Brochure. The same contingency plans and equipment will be used in this protocol. With these personnel and equipment, the researchers would be able to stabilize

a participant in the office and then transport them by ambulance if hospital admission were required.

8.0 Adverse Events

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected adverse event is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event. All AEs will be monitored by the investigators until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the investigator and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

- Mild: no limitation in normal daily activity
- Moderate: some limitation in normal daily activity
- Severe: unable to perform normal daily activity

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the trainee/subject's pre-existing condition.

2. Possibly Related

The administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.

3. Probably Related

Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

8.2 Common Expected Side Effects

Commonly expected side effects that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected side effects are defined as those most frequently reported in the literature and include: Anxiety, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Judgement, Impaired Gait/Balance, Increased Irritability, Increased personal worries or rumination, Insomnia, Jaw Clenching, Tight Jaw, Lack of Appetite, Low Mood, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Sensitivity to Cold, Thirst and Weakness.

8.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

•Results in death
•Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
•Requires or prolongs inpatient hospitalization
•Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
•Results in a congenital anomaly/birth defect
•Requires intervention to prevent permanent impairment or damage
•Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe adverse event need not be serious in nature and that a SAE need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not

result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

8.4 Adverse Event Collection

All SAEs will be collected for the duration of the protocol. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitors:

Michael C Mithoefer
Email: mmithoefer@mac.com
Telephone: 843-849-6899
Fax: 843-278-9188

Rick Doblin
Email: rick@maps.org
Telephone: 617-484-8711
Fax: 617-484-8427

Study Monitor:

Valerie Mojeiko
Email: valerie@maps.org
Telephone: 831-429-6366
Fax: 831-429-6370

Adverse events that will be collected for the duration of the protocol are:

•Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions from MDMA administration through 7 days after the MDMA administration
•Any event of concern to the participant throughout the protocol
•Any adverse event leading to withdrawal from the protocol
•Common expected side effects will be collected on the day of MDMA administration and for seven days after administration

9.0 Collection of Concomitant Medications

Participant concomitant medications will be recorded during screening. If necessary, the investigators will make plans for tapering off and discontinuing any contraindicated medication at this time, in consultation with the prescribing physician. The investigators will request information about any changes in medication just prior to the MDMA-assisted session. Medications taken during the course of the protocol, including medications taken to treat AEs will be recorded either on a non-psychotropic or

psychotropic concomitant medications CRF. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the MDMA session to avoid the possibility of interactions (the interval will be at least 5 times the particular drug's half-life). Participants may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Participants must agree that, for one week preceding the MDMA session:

a. They will refrain from taking any herbal supplement (except with prior approval of the research team).

b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).

c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).

10.0 Clinical Laboratory Assessments

The principal investigator will examine laboratory assessments gathered in screening for assessing participant eligibility. The investigator will use a list of normal ranges to conclude whether participants are eligible for the protocol, and will indicate justification for admitting participants with abnormal values.

The following laboratory assessments will be performed as a part of screening:

Serum electrolytes and the metabolic profile, which includes:

ALT/SGPT;
albumin:globulin (A:G) ratio;
albumin, serum;
alkaline phosphatase, serum;
AST/SGOT;
bilirubin, total;
BUN;
BUN:creatinine ratio;
calcium, serum;
carbon dioxide;
chloride, serum;
creatinine, serum;
globulin, total;
glucose, serum;
potassium, serum;
protein, total, serum;

sodium, serum;

CBC, which includes:
Hematocrit;
hemoglobin;
MCV;
MCH;
MCHC;
RDW;
percentage and absolute differential counts;
RBC;
red cell count;
WBC;

Urinalysis, which includes:
Color;
appearance;
specific gravity;
pH;
protein;
glucose;
ketones;
occult blood;
leukocyte esterase;
nitrite;
bilirubin;
urobilinogen;

Thyroid function, which includes:
TSH high sensitivity;
Free T4;
Free T3.

In addition, HIV serology will be performed.

A urine-dip pregnancy test for females of childbearing potential will be performed as well.

The laboratory assessments other than the urine drug screen and pregnancy test will be performed at:

Laboratory Corporation of America

1280 Johnnie Dodds Blvd, Ste 108

Mount Pleasant, SC 29464

The urine drug screen and pregnancy test will be performed at the study site.

11.0 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained prior to the start of the protocol. The clinical study site will be monitored by site visits and telephone calls to the investigator by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring visit, source data verification will be performed by a Clinical Research Associate (CRA) to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each participant enrolled. Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and 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.

12.0 Data Analysis

The primary objective of the open-label MDMA session for those who successfully completed the sponsor-designed training program for MDMA-assisted psychotherapy research is to support and expand upon the knowledge and experience gained from the training program. This goal will not involve hypothesis-testing or formal analyses. However, the investigators will maintain data for assessment of safety, including assessment of blood pressure, psychological distress, and AEs. The investigators will compute descriptive statistics for these variables.

12.1 Statistical power

Because the primary objective of this protocol is not comparative, statistical power for this protocol has not been calculated.

13.0 Informed Consent

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

Information about events during the MDMA session must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the MDMA session and of subject's legal rights, the information should include that access to original medical records and processing of coded personal information must be authorized. 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 MDMA session 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 informed consent form, and written information should receive approval from an IRB before use.

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

Because this activity is an optional element open only to those completing a sponsor developed training program of MDMA-assisted psychotherapy research, the sponsor may have access to the names of participants as enrollees in the training program. However, only the subject numbers and subject identification codes will be recorded in the CRF. Written consent to take part in the MDMA session includes giving the investigators permission to view the participant'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.

Participants can withdraw consent for participation in the protocol at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization or equivalent form, MAPS will have full access to the subject's medical records, including termination visit information. If a participant revokes only the HIPAA authorization, MAPS will have full access to all of the participant's medical records prior to the date and time of revocation.

13.1 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants in their role as research participants. Despite this, privacy cannot be guaranteed. All data will be identified only by the participant's initials on the source document and three-digit subject number numeric code. Copies of audio and video recordings intended for sharing with participants will only be marked with the participant's subject number. Any materials mailed to participants will be sent along with stamped return envelopes using the office address of the principal investigator both as main and return address. 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, researchers, and individuals analyzing data. Researchers, other than the investigators directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Each participant may, upon request, receive audio or video recordings of any of the three sessions, including the MDMA-assisted session. They may wish to review them as a means of observing and retaining information to support their own performance of MDMA-assisted psychotherapy research. The investigators will not mark these recordings with participant name or address. If session recordings are unavailable by the end of the integrative session, then the investigators will mail recordings in appropriate packages that list only investigator name and address and that maintain anonymity.

Participants will sign forms for the release of information, such as prior medical records, upon consent to permit screening for protocol enrollment.

Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. 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 greatly reduces the risk of a breach of confidentiality.

13.2 Costs to Participants

Participants will not be charged for any research activities, including any tests or assessments performed for screening, MDMA, any psychotherapy or intervention administered to the participant, or any other activity or procedure related to the MDMA session. If a participant undergoes a medical or laboratory test solely for the purpose of establishing eligibility for the MDMA session, then the sponsor will reimburse the full cost of the test or assessment. The sponsor will be responsible for payment for treating any study-related injuries. Participants will pay for any care not related to the protocol.

14.0 Record Retention

Investigators must retain all study records required by MAPS 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. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained Record Retention Investigators must retain all study records required by MAPS 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. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

15.0 Signature Page

Study title: MDMA Administration in a Therapeutic Setting in People Who have Completed the MAPS Training Program for Therapists Learning to Conduct MDMA-assisted Psychotherapy Research in Subjects with PTSD

Protocol: MT-1

I have read the foregoing protocol and agree to conduct the protocol as outlined. I agree to conduct the protocol in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

_____ _____

Investigator Signature Date

Print name:_____

On behalf of MAPS, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical protocol.

_____ _____

Sponsor Medical Monitor Signature Date

Print name:_____

References

1. Ruse, J.M., et al., *MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder: A Revised Teaching Manual Draft*. 2008, MAPS.
2. Richards, W.A., *Correspondence to sponsor*, R. Doblin, Editor. 2009.
3. Mace, C., *Personal therapy in psychiatric training.* Psychiatric Bulletin, 2001. **25**: 3-4.
4. Macran, S., W.B. Stiles, and J.A. Smith, *How does personal therapy affect therapists' practice?* Journal of Counseling Psychology, 1999. **46**: 419-431.
5. Arendsenhein, G.W., *Treatment of the Neurotic Patient, Resistant to the Usual Techniques of Psychotherapy, with Special Reference to LSD.* Top Probl Psychother, 1963. **10**: 50-7.
6. Chwelos, N., et al., *Use of d-lysergic acid diethylamide in the treatment of alcoholism.* Q J Stud Alcohol, 1959. **20**: 577-90.
7. Winkler, P. and I. Gorman, *A 40-year follow-up on Czechoslovak LSD research: LSD intoxication as a psychotherapist's didactic experience*, in *World Psychedelic Forum*. 2008: Basel, Switzerland.
8. Helminiak, D., *Letter to FDA in support of current protocol*, FDA, Editor. 2009.
9. Dumont, G.J. and R.J. Verkes, *A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers.* J Psychopharmacol, 2006. **20**: 176-87.
10. Freedman, R.R., C.E. Johanson, and M.E. Tancer, *Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2005. **183**: 248-56.
11. Hasler, F., et al., *Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA*. J Psychopharmacol, 2008.
12. Kolbrich, E.A., et al., *Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration.* J Clin Psychopharmacol, 2008. **28**: 432-40.
13. Kolbrich, E.A., et al., *Plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine after controlled oral administration to young adults.* Ther Drug Monit, 2008. **30**: 320-32.
14. Johanson, C.E., et al., *Discriminative stimulus effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans trained to discriminate among d-amphetamine, meta-chlorophenylpiperazine and placebo.* Drug Alcohol Depend, 2006. **81**: 27-36.
15. Kuypers, K.P. and J.G. Ramaekers, *Transient memory impairment after acute dose of 75mg 3.4-Methylene-dioxymethamphetamine.* J Psychopharmacol, 2005. **19**: 633-9.
16. Kuypers, K.P. and J.G. Ramaekers, *Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected.* Psychopharmacology (Berl), 2007. **189**: 557-63.
17. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving*

performance and psychomotor function. Psychopharmacology (Berl), 2006. **187**: 467-75.
18. Kuypers, K.P., M. Wingen, and J.G. Ramaekers, *Memory and mood during the night and in the morning after repeated evening doses of MDMA.* J Psychopharmacol, 2008.
19. Kuypers, K.P., et al., *Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night.* Psychopharmacology (Berl), 2007. **192**: 111-9.
20. Ramaekers, J.G., K.P. Kuypers, and N. Samyn, *Stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal.* Addiction, 2006. **101**: 1614-21.
21. Ramaekers, J.G., et al., *Involvement of Inferior Parietal Lobules in Prospective Memory Impairment during Acute MDMA (Ecstasy) Intoxication: An Event-Related fMRI Study.* Neuropsychopharmacology, 2008.
22. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation].* J Clin Psychopharmacol, 2000. **20**: 455-66.
23. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2002. **162**: 396-405.
24. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA.* Psychopharmacology (Berl), 2001. **154**: 161-8.
25. Kessler, R.C., et al., *Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**: 593-602.
26. Brunello, N., et al., *Posttraumatic stress disorder: diagnosis and epidemiology, comorbidity and social consequences, biology and treatment.* Neuropsychobiology, 2001. **43**: 150-62.
27. Norris, F.H., et al., *Epidemiology of trauma and posttraumatic stress disorder in Mexico.* J Abnorm Psychol, 2003. **112**: 646-56.
28. Perkonigg, A., et al., *Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity.* Acta Psychiatr Scand, 2000. **101**: 46-59.
29. Sareen, J., et al., *Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions.* Arch Intern Med, 2006. **166**: 2109-16.
30. Zlotnick, C., et al., *Epidemiology of trauma, post-traumatic stress disorder (PTSD) and co-morbid disorders in Chile.* Psychol Med, 2006. **36**: 1523-33.
31. Hoge, C.W., et al., *Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care.* N Engl J Med, 2004. **351**: 13-22.
32. Tanielian, T.L., L. Jaycox, and Rand Corporation., *Invisible wounds of war : psychological and cognitive injuries, their consequences, and services to assist recovery*. 2008, Santa Monica, CA: RAND. xliii, 453 p.
33. *Statement Of Jon A. Wooditch Acting Inspector General Department Of Veterans Affairs*, in *Committee On Veterans' Affairs Subcommittee On Disability Assistance And Memorial Affairs*. 2005: Washington, DC.

34. de Jong, J.T., I.H. Komproe, and M. Van Ommeren, *Common mental disorders in postconflict settings.* Lancet, 2003. **361**: 2128-30.
35. Thabet, A.A. and P. Vostanis, *Post-traumatic stress reactions in children of war.* J Child Psychol Psychiatry, 1999. **40**: 385-91.
36. Weine, S.M., et al., *Psychiatric consequences of "ethnic cleansing": clinical assessments and trauma testimonies of newly resettled Bosnian refugees.* Am J Psychiatry, 1995. **152**: 536-42.
37. Kessler, R.C., et al., *Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**: 617-27.
38. Breslau, N. and G.C. Davis, *Posttraumatic stress disorder in an urban population of young adults: risk factors for chronicity.* Am J Psychiatry, 1992. **149**: 671-5.
39. Breslau, N., *The epidemiology of posttraumatic stress disorder: what is the extent of the problem?* J Clin Psychiatry, 2001. **62 Suppl 17**: 16-22.
40. Frayne, S.M., et al., *Burden of medical illness in women with depression and posttraumatic stress disorder.* Arch Intern Med, 2004. **164**: 1306-12.
41. Foa, E.B., et al., *A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims.* J Consult Clin Psychol, 1999. **67**: 194-200.
42. Resick, P.A. and M.K. Schnicke, *Cognitive processing therapy for sexual assault victims.* J Consult Clin Psychol, 1992. **60**: 748-56.
43. Brady, K., et al., *Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial.* JAMA, 2000. **283**: 1837-44.
44. Basoglu, M., E. Salcioglu, and M. Livanou, *A randomized controlled study of single-session behavioural treatment of earthquake-related post-traumatic stress disorder using an earthquake simulator.* Psychol Med, 2007. **37**: 203-13.
45. Gerardi, M., et al., *Virtual reality exposure therapy using a virtual Iraq: case report.* J Trauma Stress, 2008. **21**: 209-13.
46. Heresco-Levy, U., et al., *Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder.* Int J Neuropsychopharmacol, 2002. **5**: 301-7.
47. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting.* J Psychoactive Drugs, 1986. **18**: 319-27.
48. Grinspoon, L. and J.B. Bakalar, *Can drugs be used to enhance the psychotherapeutic process?* Am J Psychother, 1986. **40**: 393-404.
49. Mithoefer, M., A. Mithoefer, and M. Wagner. *Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in subjects with chronic posttraumatic stress disorder*. in *24th Annual Meeting of the International Society for Traumatic Stress Studies*. 2008. Chicago, IL.
50. Farre, M., et al., *Pharmacological Interaction Between 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and Paroxetine: Pharmacological effects and pharmacokinetics.* J Pharmacol Exp Ther, 2007.
51. Hernandez-Lopez, C., et al., *3,4-Methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics.* J Pharmacol Exp Ther, 2002. **300**: 236-44.

52. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP.* Drug Alcohol Depend, 2003. **72**: 33-44.
53. Tancer, M.E. and C.E. Johanson, *The subjective effects of MDMA and mCPP in moderate MDMA users.* Drug Alcohol Depend, 2001. **65**: 97-101.
54. Vollenweider, F.X., et al., *Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers.* Neuropsychopharmacology, 1998. **19**: 241-51.
55. Battaglia, G., et al., *Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites.* Eur J Pharmacol, 1988. **149**: 159-63.
56. Setola, V., et al., *3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro.* Mol Pharmacol, 2003. **63**: 1223-9.
57. Verrico, C.D., G.M. Miller, and B.K. Madras, *MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment.* Psychopharmacology (Berl), 2007. **189**: 489-503.
58. Rosendorff, C., et al., *Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention.* Circulation, 2007. **115**: 2761-88.
59. Mas, M., et al., *Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans.* J Pharmacol Exp Ther, 1999. **290**: 136-45.
60. Pacifici, R., et al., *Paroxetine inhibits acute effects of 3,4-methylenedioxymethamphetamine on the immune system in humans.* J Pharmacol Exp Ther, 2004. **309**: 285-92.
61. Pacifici, R., et al., *Immunomodulating properties of MDMA alone and in combination with alcohol: a pilot study.* Life Sci, 1999. **65**: L309-16.
62. Pacifici, R., et al., *Immunomodulating activity of MDMA.* Ann N Y Acad Sci, 2000. **914**: 215-24.
63. Pacifici, R., et al., *Effects of repeated doses of MDMA ("ecstasy") on cell-mediated immune response in humans.* Life Sci, 2001. **69**: 2931-41.
64. Connor, T.J., J.P. Kelly, and B.E. Leonard, *An assessment of the acute effects of the serotonin releasers methylenedioxymethamphetamine, methylenedioxyamphetamine and fenfluramine on immunity in rats.* Immunopharmacology, 2000. **46**: 223-35.
65. Connor, T.J., et al., *Methylenedioxymethamphetamine-induced suppression of interleukin-1beta and tumour necrosis factor-alpha is not mediated by serotonin.* Eur J Pharmacol, 2001. **418**: 147-52.
66. Connor, T.J., A. Harkin, and J.P. Kelly, *Methylenedioxymethamphetamine suppresses production of the proinflammatory cytokine tumor necrosis factor-alpha independent of a beta-adrenoceptor-mediated increase in interleukin-10.* J Pharmacol Exp Ther, 2005. **312**: 134-43.

67. Pacifici, R., et al., *Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans.* J Pharmacol Exp Ther, 2001. **296**: 207-15.
68. Pacifici, R., et al., *Cell-mediated immune response in MDMA users after repeated dose administration: studies in controlled versus noncontrolled settings.* Ann N Y Acad Sci, 2002. **965**: 421-33.
69. Beck, J. and M. Rosenbaum, *In Pursuit of Ecstasy: The MDMA Experience*. 1994, Albany, NY: SUNY Press.
70. Fantegrossi, W.E., et al., *Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys.* Neuropsychopharmacology, 2004. **29**: 1270-81.
71. Schenk, S., et al., *Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats.* Psychopharmacology (Berl), 2003. **169**: 21-7.
72. Trigo, J.M., et al., *A reliable model of intravenous MDMA self-administration in naive mice.* Psychopharmacology (Berl), 2006. **184**: 212-20.
73. Lile, J.A., J.T. Ross, and M.A. Nader, *A comparison of the reinforcing efficacy of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") with cocaine in rhesus monkeys.* Drug Alcohol Depend, 2005. **78**: 135-40.
74. Wee, S. and W.L. Woolverton, *Self-administration of mixtures of fenfluramine and amphetamine by rhesus monkeys.* Pharmacol Biochem Behav, 2006. **84**: 337-43.
75. Huizink, A.C., et al., *Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study.* Bmj, 2006. **332**: 825-8.
76. Lieb, R., et al., *Mental disorders in ecstasy users: a prospective-longitudinal investigation.* Drug Alcohol Depend, 2002. **68**: 195-207.
77. Cottler, L.B., et al., *Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria.* Hum Psychopharmacol, 2001. **16**: 599-606.
78. von Sydow, K., et al., *Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study.* Drug Alcohol Depend, 2002. **66**: 147-59.
79. Frith, C.H., et al., *Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat.* Fundam Appl Toxicol, 1987. **9**: 110-9.
80. Baggott, M., et al., *Chemical analysis of ecstasy pills.* Jama, 2000. **284**: 2190.
81. Baggott, M.J., *Preventing problems in Ecstasy users: reduce use to reduce harm.* J Psychoactive Drugs, 2002. **34**: 145-62.
82. Cole, J.C., et al., *The content of ecstasy tablets: implications for the study of their long-term effects.* Addiction, 2002. **97**: 1531-6.
83. Liechti, M.E., I. Kunz, and H. Kupferschmidt, *Acute medical problems due to Ecstasy use. Case-series of emergency department visits.* Swiss Med Wkly, 2005. **135**: 652-7.
84. Williams, H., et al., *"Saturday night fever": ecstasy related problems in a London accident and emergency department.* J Accid Emerg Med, 1998. **15**: 322-6.
85. Cole, J.C. and H.R. Sumnall, *The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA).* Neurosci Biobehav Rev, 2003. **27**: 199-217.

86. Green, A.R., et al., *The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy").* Pharmacol Rev, 2003. **55**: 463-508.
87. O'Callaghan, J.P. and D.B. Miller, *Neurotoxicity profiles of substituted amphetamines in the C57BL/6J mouse.* J Pharmacol Exp Ther, 1994. **270**: 741-51.
88. Hatzidimitriou, G., U.D. McCann, and G.A. Ricaurte, *Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery.* J Neurosci, 1999. **19**: 5096-107.
89. Miller, D.B. and J.P. O'Callaghan, *Neurotoxicity of d-amphetamine in the C57BL/6J and CD-1 mouse. Interactions with stress and the adrenal system.* Ann N Y Acad Sci, 1996. **801**: 148-67.
90. Molliver, M.E., et al., *Neurotoxicity of MDMA and related compounds: anatomic studies.* Ann N Y Acad Sci, 1990. **600**: 649-61; discussion 661-4.
91. Sabol, K.E., et al., *Amphetamine analogs have differential effects on DRL 36-s schedule performance.* Psychopharmacology (Berl), 1995. **121**: 57-65.
92. Seiden, L.S. and K.E. Sabol, *Methamphetamine and methylenedioxymethamphetamine neurotoxicity: possible mechanisms of cell destruction.* NIDA Res Monogr, 1996. **163**: 251-76.
93. Mechan, A., et al., *Pharmacokinetic profile of single and repeated oral doses of MDMA in squirrel monkeys: relationship to lasting effects on brain serotonin neurons.* Neuropsychopharmacology, 2006. **31**: 339-50.
94. Baumann, M.H., X. Wang, and R.B. Rothman, *3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings.* Psychopharmacology (Berl), 2007. **189**: 407-24.
95. Banks, M.L., et al., *Effects of Cocaine and MDMA Self-Administration on Serotonin Transporter Availability in Monkeys.* Neuropsychopharmacology, 2008. **33**: 219-25.
96. Wang, J., et al., *Respondent-driven sampling to recruit MDMA users: a methodological assessment.* Drug Alcohol Depend, 2005. **78**: 147-57.
97. Wang, X., et al., *3,4-methylenedioxymethamphetamine (MDMA) administration to rats decreases brain tissue serotonin but not serotonin transporter protein and glial fibrillary acidic protein.* Synapse, 2004. **53**: 240-8.
98. McCann, U.D. and G.A. Ricaurte, *Caveat emptor: editors beware.* Neuropsychopharmacology, 2001. **24**: 333-6.
99. Cole, J.C. and H.R. Sumnall, *Altered states: the clinical effects of Ecstasy.* Pharmacol Ther, 2003. **98**: 35-58.
100. McCann, U.D., et al., *Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB.* Neuropsychopharmacology, 2005. **30**: 1741-50.
101. Reneman, L., et al., *Neuroimaging findings with MDMA/ecstasy: technical aspects, conceptual issues and future prospects.* J Psychopharmacol, 2006. **20**: 164-75.
102. Thomasius, R., et al., *Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective.* J Psychopharmacol, 2006. **20**: 211-25.

103. Laws, K.R. and J. Kokkalis, *Ecstasy (MDMA) and memory function: a meta-analytic update.* Hum Psychopharmacol, 2007.
104. Zakzanis, K.K., Z. Campbell, and D. Jovanovski, *The neuropsychology of ecstasy (MDMA) use: a quantitative review.* Hum Psychopharmacol, 2007. **22**: 427-35.
105. Gouzoulis-Mayfrank, E., et al., *Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users.* Prog Neuropsychopharmacol Biol Psychiatry, 2003. **27**: 819-27.
106. Halpern, J.H., et al., *Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs.* Drug Alcohol Depend, 2004. **75**: 135-47.
107. Hoshi, R., et al., *Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naive controls.* Psychopharmacology (Berl), 2007. **194**: 371-9.
108. Roiser, J.P., R.D. Rogers, and B.J. Sahakian, *Neuropsychological function in ecstasy users: a study controlling for polydrug use.* Psychopharmacology (Berl), 2007. **189**: 505-16.
109. Gouzoulis-Mayfrank, E., et al., *Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use.* Drug Alcohol Depend, 2005. **78**: 317-23.
110. Daumann, J., et al., *Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation.* Psychopharmacology (Berl), 2004. **173**: 398-404.
111. Morgan, M.J., et al., *Elevated impulsivity and impaired decision-making in abstinent Ecstasy (MDMA) users compared to polydrug and drug-naive controls.* Neuropsychopharmacology, 2006. **31**: 1562-73.
112. Sumnall, H.R. and J.C. Cole, *Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis.* J Psychopharmacol, 2005. **19**: 84-92.
113. Sumnall, H.R., G.F. Wagstaff, and J.C. Cole, *Self-reported psychopathology in polydrug users.* J Psychopharmacol, 2004. **18**: 75-82.
114. Medina, K.L. and P.K. Shear, *Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: Contributions of polydrug use.* Drug Alcohol Depend, 2006.
115. Scholey, A.B., et al., *Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a WWW study.* Addict Behav, 2004. **29**: 743-52.
116. Jager, G., et al., *Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study.* Psychopharmacology (Berl), 2007. **193**: 403-14.
117. de Win, M.M., et al., *A Prospective Cohort Study on Sustained Effects of Low-Dose Ecstasy Use on the Brain in New Ecstasy Users.* Neuropsychopharmacology, 2007. **32**: 458-470.
118. de Win, M.M., et al., *Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study.* J Psychopharmacol, 2006. **20**: 226-35.

119. Schilt, T., et al., *Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study.* Arch Gen Psychiatry, 2007. **64**: 728-36.
120. de Win, M.M., et al., *Mood disorders and serotonin transporter density in ecstasy users--the influence of long-term abstention, dose, and gender.* Psychopharmacology (Berl), 2004. **173**: 376-82.
121. Jager, G., et al., *Assessment of cognitive brain function in ecstasy users and contributions of other drugs of abuse: results from an FMRI study.* Neuropsychopharmacology, 2008. **33**: 247-58.
122. Reneman, L., et al., *Memory function and serotonin transporter promoter gene polymorphism in ecstasy (MDMA) users.* J Psychopharmacol, 2006. **20**: 389-99.
123. Schilt, T., et al., *Specific effects of ecstasy and other illicit drugs on cognition in poly-substance users.* Psychol Med, 2008. **38**: 1309-17.
124. Schilt, T., et al., *Decision making as a predictor of first ecstasy use: a prospective study.* Psychopharmacology (Berl), 2009. **203**: 519-27.
125. Adamson, S., *Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances*. 1985, San Francisco CA: Four Trees Publications.
126. Gasser, P., *Psycholytic therapy with MDMA and LSD in Switzerland.* MAPS Bulletin, 1994. **5**: 3-7.
127. Metzner, R. and S. Adamson, *sing MDMA in healing, psychotherapy and spiritual practice*, in *cstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA.*, H. J, Editor. 2001, Inner Traditions: Rochester VT. p. 182-207.
128. Widmer, S., *Listening into the heart of things: The awakening of love: On MDMA and LSD: The undesired psychotherapy. .* 1998, Gerolfingen, Switzerland: Basic Editions.
129. Ryan, T.J., et al., *1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction).* J Am Coll Cardiol, 1999. **34**: 890-911.
130. *Practice advisory: thrombolytic therapy for acute ischemic stroke--summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology.* Neurology, 1996. **47**: 835-9.
131. Adams, H.P., Jr., et al., *Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.* Stroke, 2007. **38**: 1655-711.

Appendix A: Prevention and Response to Possible Serious Adverse Events

Risk Mitigation

Information from a considerable body of research indicates that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low [9], see also Section 6 of the "Investigator's Brochure." Psychiatrists in the U.S. and Europe reported administering MDMA to at least a thousand patients before the drug was made illegal without any drug-related SAEs occurring during sessions [47, 125-128]. There have been no drug-related SAEs during the course of a study of MDMA-assisted psychotherapy in people with PTSD under the direction of the principal investigator for the proposed protocol. Procedures for monitoring for toxicity and risks for the training program will be similar to those employed in the study of MDMA-assisted psychotherapy in people with PTSD.

Although serious untoward reactions are unlikely, the researchers will closely and continuously monitor participants during the MDMA session. Throughout all sessions, participants will be attended by the investigators, a psychiatrist who is board-certified in emergency medicine and internal medicine as well as psychiatry and who maintains Advanced Cardiac Life Support certification, and a psychiatric nurse with experience working on a cardiac care unit before going into psychiatric nursing. The principal investigator and assisting investigator will thus provide a team of an experienced emergency physician and a registered nurse to respond in the unlikely event of a medical emergency.

The listed means of minimizing the likelihood of any of the SAEs that are reported to occur in ecstasy users will be similar to the procedures and strategies employed in the current study of MDMA-assisted psychotherapy in people with PTSD.

Psychological Distress

Reports of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that some people receiving MDMA in a therapeutic context experienced periods of increased anxiety and even panic. Psychological distress may arise at any time after the onset of the effects of MDMA until the last effects have dissipated (approximately 3 to 5 hours after drug administration), with anxiety or distress potentially lasting for as little as 15 minutes to as long as 5 hours. It is also possible that anxiety or other psychological distress may arise after the acute effects of the MDMA have subsided. Participants will be individuals without current psychiatric disorders who have completed a sponsor-developed training program on MDMA-assisted psychotherapy research. The likelihood of their experiencing clinically significant anxiety during an MDMA session is lower than for people with current psychiatric problems. It is still possible, though unlikely, that MDMA may spark intense psychological distress or a panic response.

The potential for destabilizing psychological distress will be minimized by excluding people who might be more vulnerable to psychological distress as stated in the exclusion criteria and by creating an atmosphere of trust before and during the MDMA session, and by close monitoring and daily contact for a week (or more if necessary) after the MDMA-assisted session.

At the end of the 6–8 hour experimental session, if the participant is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

- If the participant is anxious, agitated, in danger of any self-harm or is suicidal at the end of the MDMA session, the investigators will remain with the participant for at least two more hours. During this time, the investigators will employ affect management techniques, will talk with the participant to help him or her gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the introductory session. If this situation should occur during an integrative therapy session, at least one of the investigators will be available to stay with the participant for at least two additional hours.

- If a participant remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period the principal investigator will decide between one of two options:

A. A psychiatric nurse, therapeutic assistant or therapist will stay with the subject until the time of his or her appointment with investigators the next day. The investigators will then meet with the subject daily until the period of destabilization has passed. At any time during this process, the principal investigator may make the clinical judgment to proceed to option B.

B. Hospitalization for stabilization.

Participants hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigator will carefully evaluate the participant's emotional status. The investigators will submit an SAE report to the IRB and the FDA in cases of drug-related hospitalization.

For those subjects engaged in an on-going therapeutic relationship with a psychotherapist or psychiatrist, the participant's outside therapists will be involved in the management of any psychiatric complications.

In the event of a participant's experiencing severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an MDMA session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." This

medication will be captured on a psychotropic concomitant medications CRF page. If a participant should become psychotic or suicidal, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility of their choice. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Means of monitoring for and preventing possible risks of MDMA other than the cardiovascular risks and psychological distress are described in detail below.

Angina or Myocardial infarction

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in individuals who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have EKG evidence of AMI [129](J Am Coll Cardiol 34:890, 1999).

Stroke

If any participant has neurologic deficits, whether or not they are associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be transported to the hospital for a head CT scan and further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the 3 hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [130, 131].

Hyponatremia

History of hyponatremia or detection of hyponatremia on initial physical examination will be cause for exclusion from the proposed protocol. Participants will be given primarily electrolyte solutions such as Gatorade instead of water in order to decrease the likelihood of dilutional hyponatremia. They will not be allowed to drink more than 3 L. of fluids, and fluid intake will be appropriately spread out across the session. If there are any signs or symptoms of hyponatremia, a stat serum sodium will be drawn and fluids will be withheld until the results are obtained. If the serum sodium is less than 125mEq/L, serum and urine osmolality and sodium will be measured, and the subject will be transported to the East Cooper Medical Center, where further intervention can be provided.

Hyperthermia

Body temperature will be taken every 60 to 90 minutes throughout each experimental session. If temperature rises more than 1° Celsius (C), attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the subject. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, ice packs will be used, blood will be drawn for stat CBC, electrolytes, BUN, creatinine, glucose, creatine phosphokinase (CPK), prothrombin time (PT), partial thromboplastin time (PTT), platelets and liver enzymes, and urine will be collected for urinalysis. If there are significant abnormalities in these tests, if the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity the participant will be transferred to the intensive care unit at the East Cooper Medical Center.