6.2 Visit Descriptions

6.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1)

After giving written informed consent each participant will be assigned a screening number. 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 (ECG), clinical laboratory assessments to determine study eligibility (see 10.0 for list of laboratory tests). In addition, Human Immunodeficiency Virus (HIV) serology will be performed. If there is a confirmed positive HIV serology it will be kept confidential with the exception of reporting to the South Carolina Department of Health as required by law, with the Department of Health informing the home state of any individual not residing in South Carolina. Appropriate referral for counseling and treatment 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. If it is determined that the participant has Hepatitis C or well-controlled hypertension, further evaluation will be performed as described in section 6.0.

After eligibility is confirmed the participant will be considered enrolled and will be issued a subject number and contacted to schedule the introductory non-drug psychotherapy sessions and first experimental session. Any participant who must discontinue a medication will, after consultation with the prescribing physician, be given a schedule to begin tapering off that medication so washout will be completed before the first experimental session, with the interval between the start of washout and the first experimental session being at least five times the drug's half-life. The first experimental session will be scheduled to occur after washout is complete.

A blinded independent rater who will not be present during any of the therapy sessions will administer the CAPS and assess the participant on the GAF. The C-SSRS will also be administered at screening to assess suicide risk. The participant will complete the BDI and PTGI-C.

The entire visit should take between 1.5 and 2.5 hours. Screening may take place over more than one day and up to one month prior to visit 1.

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.

6.2.2 Preparatory Sessions (Visits 2-4)

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 adhered to the schedule for tapering off medications.

The participant will undergo three 90-minute preparatory non-drug psychotherapy sessions with the investigators at their offices. During these sessions the investigators will gather more detailed history, answer any questions the participant may have, and work toward forming a strong therapeutic alliance. The participant and investigators will discuss goals for the MDMA sessions. They will review the procedures and therapeutic approach, following standard procedures and techniques discussed in the sponsor-developed treatment manual. The investigators will prepare the participant for the upcoming experimental sessions and promote an atmosphere of safety in which to confront traumatic experiences and powerful emotions.

During the third and last introductory session, 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.

Unless a participant is still undergoing medication washout, participants will complete the C-SSRS just prior to beginning the second preparatory session. Participants still undergoing medication washout will complete the C-SSRS during the third preparatory session or at a point after washout is complete.

The attendant, described below, will remain with the participant during each overnight stay after each MDMA-assisted psychotherapy session. He or she will be of the same sex as the participant, will have a healthcare background, and will undergo specific training for the role. 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. Such an individual will not replace the night-time attendant. Introductory sessions will be recorded to audio and video, and participants can receive copies of one or more introductory sessions upon request. All SAEs will be recorded from the time the participant is enrolled at Visit 1.

6.2.3 MDMA Session (Visits 5, 9, and 13)

All participants will receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Each experimental session will last approximately eight hours followed by an overnight stay at the study site. Experimental

sessions will be conducted by the male and female co-therapist team. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except drug dose will be the same for participants assigned to the full, medium and active placebo dose conditions.

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, with confirmation of eligibility including a urine drug screening and, if appropriate, a urine pregnancy test. 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.

Before MDMA is administered, the therapists and participant will discuss and review the participant's goals, intentions and concerns and some of the commonly experienced effects of MDMA. Participants will complete the SUD just prior to initial dose administration.

At approximately 10:00 A.M., participants will receive the initial dose of 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. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material [81-83]. The investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of their inner experience, in accordance with the principles of MAPS' treatment manual [84]. Water and electrolyte containing fluids will be available ad lib throughout the session within the limits described in Appendix A. Food will be available during the latter part of the session. The investigators will record the entire session to video and audio. Participants may receive a copy of audio or video recordings of at least one experimental session upon request. 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. After the first hour, if the participant has not spoken spontaneously, the investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the investigators will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging.

Suicidality will be assessed with the C-SSRS twice during each experimental session (approximately one hour before and five to six hours after drug administration),

Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first 4 hours of the MDMA-assisted session and every 30

minutes for another 2 hours. More frequent measures will be taken as described in section 6.1.2 if the established thresholds are exceeded, or if the subject has a diagnosis of hypertension. Participant body temperature will be measured via tympanic thermometer every 60-90 minutes. Participants will complete the SUD every 90 minutes, until the session is over, allowing a window of plus/minus 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the investigators can make a greater number of SUD measurements as their clinical judgment dictates. The investigators will record any spontaneously reported side effects during the session

A supplemental dose half the size of the initial dose will be administered 1.5 to 2.5 hours after the initial dose upon mutual agreement between the investigators and participant.

Approximately six hours after drug administration, the investigators will administer the C-SSRS.

If there is a support-individual who has previously been asked and has agreed to be present during part or all of the MDMA session, that person may arrive during the session at whatever time has been agreed upon, but will wait in the waiting room until brought back to the session room by one of the therapists.

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 audio and video when they have established that the participant returned to baseline function or is very close to doing so. Both of the investigators conducting psychotherapy reside near the study site and one or both can quickly return to the site if necessary. Throughout the study, at least one of the investigators, or a physician who is covering for them if they are not available, will remain available to participants via 24-hour cellular telephone.

The participant will remain at the study site overnight, in a comfortably furnished suite that allows for accompaniment by a significant other, and the attendant. The attendant will remain in the building during the overnight stay, even if a significant other is present. The attendant will attend to the subject's needs such as food and fluids during the overnight stay. The attendant will be an individual with previous training or experience in supporting individuals in psychological distress. The attendant may be anyone with some training or background in health care, particularly in psychiatric care. If there is an emergency or the participant needs additional support, the attendant can contact the investigators. The participant and if applicable, his or her significant other, will also receive contact information for the investigators during the overnight stay in the case of an emergency or request for additional support. Participants will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

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 occurring during study enrollment will be recorded.

6.2.4 Integrative Sessions 24 Hours after Experimental Session (Visits 6, 10, 14)

On the morning after the MDMA session, the participant will meet with both investigators during a 90-minute integrative psychotherapy session. Participants will complete the C-SSRS just prior to beginning each integrative session. At the beginning of this session, the participant and both investigators conducting psychotherapy will indicate their beliefs concerning participant condition assignment. The participant and investigator will then discuss and review events, thoughts, feelings and memories that occurred during the experimental session. If necessary, the investigators will help the participant to reduce any residual psychological distress he or she may be experiencing. The therapists will also encourage exploration of any new insights and perspectives resulting from states of acceptance, feelings of intimacy, and reduced fear that may have occurred during MDMA sessions and that may be applicable to emotionally distressing situations in everyday life. The investigators will be supportive, validating the MDMA experience and facilitating understanding and emotional clearing. The investigators will assess participant mental health and the presence of any remaining side effects during integrative psychotherapy sessions. Integrative psychotherapy sessions can also serve as an opportunity for the investigators to gather information in an unstructured manner about the effects of MDMA on the participant.

After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the participant is unable to locate an individual to take him or her home, the investigators will arrange an alternative means of transportation. The entire integrative psychotherapy session will be recorded to audio and video. Participants may receive copies of this session upon request. Therapists will be accessible if the participant needs support outside the scheduled integration sessions.

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 Telephone Contact for Seven days after an Experimental Session

Starting on the day of the non-drug integrative psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone daily for one week. The 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 or difficulties integrating their experience and to assess participant well-being. Additional telephone contact can be initiated at the request of the investigators or participant. 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. On the second and seventh day of telephone contact, the C-SSRS will be administered to monitor for suicide risk.

6.2.6 Integrative Psychotherapy Between Experimental Sessions

The participant will have 60 to 90-minute scheduled non-drug psychotherapy sessions with both psychotherapist investigators during the interval between the first and second experimental session, between the second and third experimental sessions and after the third experimental session (See Time and Events Table). The investigators may conduct more sessions if they and the participant deem it necessary. The purpose of these sessions is to provide continued support for the participant as she or he considers his or her experiences during the experimental sessions and strives to integrate them into their lives. The investigators will use clinical judgment to assess the participant's psychological well-being during this period of time. Suicidality will be assessed with the C-SSRS. Each integrative session will be recorded to audio and video, and participants may receive a copy of one or more integrative sessions upon request. If there are any indications of continuing anxiety or distress, the investigators may arrange to address it in a specially scheduled non-drug therapy session, through continuing telephone contact, or at the next regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study.

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. If an integrative session falls within the seven-day period of telephone contact, it will replace the day of telephone contact, and spontaneously reported side effects will be recorded as reported during the session. Any spontaneously reported effects occurring outside of this period will be recorded as AEs. All SAEs will be recorded.

Evaluation One Month After the Second Experimental Session

Participants will meet with the independent rater for a 90 to 120-minute evaluation one month after the second experimental session and prior to the third experimental session. The independent rater will administer the CAPS, BDI, PTGI-C, and assess participant quality of life with the GAF. Suicidality will be assessed with the C-SSRS. All SAEs will be recorded.

6.2.7 Evaluation Two Months after the Third Experimental Session

The final evaluation in the double-blind portion of the study will occur two months after the third experimental session. Participants will meet the independent rater for 90 to 120 minutes. The independent rater will administer the CAPS, BDI, PTGI-C and C-SSRS, and the independent rater will assess the participant on the GAF. The measures are described earlier in "Assessments and Measures." All SAEs will be recorded.

6.2.8 Unblinding and Opportunity for Participants in Active Placebo and Medium Dosage Condition to Enroll in Open-Label Study Segment ("Stage 2")

After completing all assessments and measures at the evaluation two months after the third experimental session, the participant will meet with the investigators for approximately one hour, and the blind will be broken for that individual. Participants assigned to the full-dose condition and participants assigned to the other conditions who

decline enrolling in Stage 2 will complete the Responses to Research Participation Questionnaire. Participants who are not enrolled in Stage 2 may return to taking psychiatric medications. The independent rater will remain blind to condition assignment at this time.

After unblinding, the investigators will provide Stage 2 consent materials to all participants who had been assigned to the active placebo and medium-dose conditions. Participants who elect to enroll in Stage 2 will undergo a course of therapy and evaluation nearly identical to the randomized study, but with full-dose MDMA given in an open-label context. They must give written, informed consent before enrolling in Stage 2.

6.2.9 Open-Label Study Segment for Active Placebo and Medium Dosage Participants ("Stage 2")

Participants assigned to receive active placebo or medium-dose MDMA during the randomized study segment will undergo three open-label MDMA-assisted psychotherapy sessions that follow a course and schedule similar to the randomized study except that participants undergo one instead of three introductory sessions. After giving written informed consent, participants enrolled in Stage 2 will meet with both investigators conducting psychotherapy for a single review and re-introductory psychotherapy session before the first open-label MDMA-assisted psychotherapy session. Spontaneously reported side effects, AEs and SAEs will be collected and reported in the same manner as during the randomized study segment.

6.2.10 Assessment Two Months after Third Open-Label Session

All participants in Stage 2 will be assessed by the independent rater two months after their final open-label session. At that visit, the independent rater will administer the CAPS, and complete the GAF, and participants will complete the BDI, PTGI-C, the C-SSRS and the RRPQ. From this point forward subjects will no longer be required to refrain from taking psychotropic medications. All SAEs will be recorded.

6.2.11 Evaluation 12 Months After Final Experimental Or Open Label] Session

All participants who completed Stage 1 only will be evaluated 12 months after their third experimental session, and all participants who completed Stage 2 will be evaluated 12 months after their third open-label MDMA-assisted psychotherapy session. The independent rater will administer the CAPS and complete the GAF. Suicidality will be assessed with the C-SSRS. Participants will also complete a questionnaire assessing positive and negative long-term effects of the study. Outcome measures will either be completed over the telephone or at the study site, and the participant will return self-report questionnaires in envelopes supplied by the investigators with the study site listed both as the mailing and return address.

6.3 Removal of Participants from the Study

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 protocol that are

critical for safety or necessary for the scientific integrity of the study. If the investigator withdraws a participant from the study, the investigators will explain the reason for withdrawing the participant.

Participants who withdraw 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 the Study

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform the study subjects and will arrange appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor, will be treated in accordance with federal and local regulations. Participants will still receive recordings of sessions if they request them.

7.0 Risks Of Study Participation

7.1 Screening

Medical data will be collected via history and physical examination and measurement of vital signs, laboratory tests, and ECG. If indicated, additional procedures such as exercise tests and ultrasound imaging will be administered. Submitting to a full medical examination may be time consuming, and may be distressing or uncomfortable for some. Because medical examinations are part of the screening procedure, they cannot be omitted from the study design.

Psychological assessments will be obtained through interviews. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The investigators have experience working with people with PTSD, and they will seek to reduce anxiety and distress during these interviews.

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 and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

During non-drug and MDMA-assisted psychotherapy sessions, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses to recalling and speaking

about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy and experimental sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (MDMA-assisted psychotherapy), and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

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

All psychotherapy sessions will be recorded to audio and video and participants may have access to recordings if they request them. Participants may feel uncomfortable with having their sessions recorded. The recordings will be used for developing a manualized form of MDMA-assisted psychotherapy to be used in future research, and participants may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Participants will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by investigators, trainees or regulatory agencies.

7.4 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 (IB).

MDMA may produce mild alterations in sensory perception and altered perception of time [40, 59, 67]. Women may be more sensitive to these effects than men [61]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [46].

7.4.1 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. Participants enrolled in controlled trials with MDMA (approximately 5% per trial) have had elevations in blood pressure above 200/100 mmHg or above a cut-off of 140/90 mmHg [67, 85]. 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 (160 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 Dr. Michael Mithoefer, the Principal Investigator who recently conducted a study of MDMA-assisted psychotherapy in 21 participants with PTSD, demonstrates 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.

7.4.2 Psychological Distress

Psychological distress from MDMA could arise at any time 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 the investigator, with occasional use of benzodiazepines for anxiety. In the proposed study, participants will have volunteered for the sessions with the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, anxiety, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. Investigator responses to psychological distress are discussed in detail in Appendix A.

Less commonly, mild anxiety and depressed mood are reported 1–3 days after MDMA administration [60, 61, and see the IB]. At least some of the physiological or psychological side effects listed above are very likely to occur. Proper preparation and follow-up support will reduce the impact of acute or sub-acute side effects, so that participants are not likely to be unduly troubled by them.

7.4.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body Temperature [61], 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), or 37.7 Celsius (C) 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.

7.4.4 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 [86-88]. 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 [89-91]. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [88, 92]. 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 [93, 94], 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 [94]. 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.

7.4.5 Abuse Liability

MDMA was classified as a Schedule 1 compound in 1985, 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 defined to include drugs with high abuse potential and no known medical use [95]. 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 [96-98]. However, monkeys will "pay" higher prices in lever presses for psychostimulants than they will for MDMA [99, 100]. 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 [101, 102], though studies of non-representative samples have reported higher rates of dependence [103]. Most regular ecstasy users report taking ecstasy no more often than once a week [104]. 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.

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) [61]. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Mithoefer reported that few participants in the study of MDMA-assisted psychotherapy in people with PTSD reported desiring to take MDMA in an unsupervised setting.

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.

7.4.6 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 [105], 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 [106-108], 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 [109, 110]. In the proposed clinical protocol, study eligibility is intended to reduce the likelihood of many serious adverse events. Participants will be carefully monitored for signs and symptoms of these events and will be offered supportive psychotherapy and other forms of support determined to

be necessary by the Principal Investigator. Contingency plans for responding to these events are described in Appendix A.

7.4.7 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 [111-113], with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin [114]. Similar changes can be induced by methamphetamine and other psychostimulants [115-117]. Previous studies in nonhuman primates overestimated human-equivalent doses [118], and previous studies in rodents may also have overestimated human-equivalent doses [119]. 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 [96, 120-122]. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [123]. 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 [124]. 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 [125-127], 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 [124, 128, 129]. 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 [130-133], though other studies also reported that abstinence from ecstasy did not attenuate memory impairment in heavy users [127, 134]. 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[135-138]. 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 [101, 102], and it appears that polydrug use may contribute to this association [135, 138-140]. 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 [141-144]. The team also performed studies expressly in heavy ecstasy users [145-148]. 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 [141, 142]. 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 [141]. 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 of an average of 3.2 tablets, with non-user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users [141]. It is notable that the study examining SERT sites and cerebral blood flow did not employ non-user controls, 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 women who decided to use ecstasy had higher impulsivity scores prior to use. [149]. 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 each MDMA-assisted psychotherapy session.

7.4.8 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 [150, 151]. 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 experimental session and must agree to use birth control during the period of the protocol.

7.5 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. Intravenous fluids, antiarrhythmic drugs, antihypertensive drugs (such as nitroprusside and labetolol), injectable epinephrine and other pressor agents, 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. 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). As is now common practice in emergency departments, an automatic blood pressure pump will be used in place of intraarterial blood pressure monitoring equipment. 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 the exception of the fact that there will not be an additional nurse on site for this study. In the unlikely event of cardiac arrest, the researchers will follow the American Heart Association guidelines for 2-person BLS for Healthcare Providers (including defibrillation with an automated external defibrillator (AED) until the arrival of EMS, at which time ACLS procedures will be instituted. With these personnel and equipment, the researchers, in conjunction with EMS if necessary would be able to begin treatment in the office and then transport the participant by ambulance if hospital admission were required.

8.0 Adverse Events

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

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 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 Judgment, 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. Other common side effects in preliminary data from the initial study of MDMA-assisted psychotherapy in people with PTSD include gastrointestinal discomfort or diarrhea in approximately 3.3% participants receiving MDMA.

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 a study-related 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:

Julie Holland, MD
NYU School of Medicine
[redacted]

Study Monitor:

Valerie Mojeiko
Email: valerie@maps.org
[redacted]

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

All medications, over the counter (OTC) and prescription will be collected from screening through 7 days after the last MDMA session. From 7 days after the last MDMA session through study termination only prescription or OTC medications taken to treat AEs will be collected.

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 each MDMA-assisted psychotherapy session. Medications taken during the course of the protocol, including medications taken to treat AEs will be recorded on a 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 and Hepatitis C** 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 investigators will examine CAPS and GAF scores at baseline, one month after session 2, and two months after session 3 in active placebo, medium-dose and full-dose conditions. The investigators will record peak blood pressure, heart rate and body

temperature for participants during every session. Descriptive statistics will be calculated for all measurements overall and within the three dose conditions. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Effect size of the three doses for all outcome measures for Stage 1, Stage 2, and one year post will be estimated using Cohen's techniques.

The sample selection is expected to produce acceptably homogeneous groups due to their all being veterans who served in the US Armed Forces diagnosed with PTSD and with CAPS scores of at least 50. There is no expectation that conditions will differ in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression.

Multivariate analysis of variance will be used to compare the full dose and non-full dose conditions for change in CAPS, BDI, PTGI-C and GAF scores. If a significant result is found, post hoc analysis of variance will be conducted for CAPS, BDI, PTGI-C and GAF scores separately. Further, if significant results are found for either CAPS, BDI, or GAF scores, post hoc t-tests will be conducted to determine explicitly where the differences occurred.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The investigators will informally or formally compare peak blood pressure, heart rate and body temperature for participants after sessions using active placebo, medium-dose and full-dose MDMA.

12.1 Statistical power

The literature does not provide an estimate of the effect size for change in CAPS after sessions using a medium-dose or for change in GAF scores under the proposed dosing regimen. The proposed study will provide these important estimates.

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 evaluation, preparatory, MDMA and integrative psychotherapy sessions, 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. A second informed consent form (ICF) will be

obtained from all medium and active-placebo dose subjects who elect to go through the open-label Stage 2 process.

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.

Written consent to take part in the study 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.

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.

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. 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. Despite this, privacy cannot be guaranteed. Except for the screening log, the informed consent and a subject contact information sheet which will be stored separately from other documents, all data will be identified only by the participant's initials on the source document and three-digit subject number numeric code. If past medical records are needed participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. 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.

All psychotherapy sessions will be recorded to video and audio. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted psychotherapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Full names and addresses, if they appear in these recordings, will be edited out of the recording before the tape is seen by anyone other than the study participant, the investigators present at the session, and the designated audio/video technician who has signed a confidentiality agreement..

Any use of recordings for purposes other than research or training (eg: a documentary film) may occur only with separate written informed consent of the participant obtained after study participation is complete.

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

There will be no costs to the study participants. The sponsor will cover all costs of study participation. Charges for treatment of the participant's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the participant or to the participant him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of participants who previously received therapy from the Principal Investigator and who will continue to receive ongoing treatment that is not related to participating in the study.

13.3 Treatment and Compensation of Study Related Injury

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. Most study-related emergencies can be treated by the investigators as described under "Medical Emergencies" (Section 7.5) and within Appendix A. If the investigator cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital, East Cooper Medical Center.

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.

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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 [40], 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 [33, 35, 58, 152, 153]. 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, nor in any other ongoing sponsor-supported study of MDMA-assisted psychotherapy in people with PTSD.

Although serious untoward reactions are unlikely, the researchers will closely and continuously monitor participants during an experimental 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 (ACLS) certification, and a psychiatric nurse who will maintain Basic Life Support (BLS) certification. 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. In the unlikely event of cardiac arrest, they will follow the American Heart Association guidelines for 2-person BLS for Healthcare Providers (including defibrillation with an automated external defibrillator (AED) until the arrival of EMS, at which time ACLS procedures will be instituted.

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. In the proposed study, participants will have the intention of confronting and working on their traumatic experiences and accepting and working through difficult and painful emotions. Hence, signs of psychological distress, panic or other unpleasant psychological reactions are possible. Psychological distress could 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.

The potential for destabilizing psychological distress will be minimized in several ways. in several ways. During the preparatory sessions, participants will be made aware of the

fact that difficult emotions, including grief, rage and fear or panic, may arise during experimental sessions. Every effort will be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session, including empathic listening on the part of the investigators and performance of diaphragmatic breathing by participants. Risks will be reduced by excluding people who might be more vulnerable to destabilizing psychological distress (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders), by preparing people before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring, by daily contact with subjects for the period of a week after the experimental session, and by providing non-drug integrative psychotherapy sessions. Subjects will remain in the offices of the Principal Investigator for the evening and night immediately following each experimental session. The study site will be staffed by a trained attendant to respond to the needs of the subject. The investigators will offer specialized training for all attendants to prepare them for being supportive but not intrusive as subjects rest and reflect on the day's experience. The attendant will be instructed to contact the investigator upon request or at the appearance of signs of a potential adverse event. The overnight stay in a private room in the study site and the presence of the attendant should further reduce psychological distress. There is also the possibility of psychological distress during the integration period following experimental sessions unrelated to direct effects of the experimental compound. Such distress occurs commonly in Prolonged Exposure, EMDR and other therapies for PTSD.

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 them express their feelings or 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. 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 will be given 162 mg of chewable aspirin once 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 [154].

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 [155, 156].

Hyponatremia

History of hyponatremia or detection of hyponatremia on initial laboratory 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.

Appendix B: Audio and Video Recording

Recording to video will be done with two cameras operated remotely by the investigators, already present as co-therapists for the experimental and non-drug psychotherapy sessions. One camera will be adjusted to capture a fairly tight shot of the subject, including full-face shots and partial or full body shots. The other will capture a wider view including the subject and the two investigators. Two copies of the video will be made routinely, one to be stored by the investigators, and the other by the sponsor. Both will be kept in locked cabinets in secure locations. A third copy of any video recording can be made for any subject who requests it.

Full names and addresses are unlikely to appear on the video or audio tapes. However, if they do, they will be edited out of the recording before the tape is seen by anyone other than the study participant and the investigators present at the session. Facial images will not be removed from the copy of the video recording to be viewed by the sponsor or investigators for review of the therapeutic process and for manual development.

Audio recording of experimental and non-drug psychotherapy sessions will be done using a digital recording device controlled by one of the investigators, with control allowing him to stop or start recording. The recordings will be transferred to an external hard drive that will be kept in a locked cabinet. The recordings will then be burned onto CDs. One copy will be stored by the investigators in a locked cabinet, another copy will be sent to the sponsor and will also be stored in a locked cabinet at the location of the sponsor. An additional audio recording can be made of any psychotherapy session. The purpose of this is to enable the participants to have a recording for themselves at the end of each experimental session, rather than having to wait until the CDs are made by the investigators. Part or all of these recordings may be viewed by people training to perform MDMA-assisted psychotherapy for sponsor-supported studies.