copernicus group independent review board

Approved:

SUBJECT INFORMATION AND CONSENT FORM AND HIPAA AUTHORIZATION

Study Title:	A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
Protocol #:	MP-12
Study Sponsor:	Multidisciplinary Association for Psychedelic Studies (MAPS) 1115 Mission St. Santa Cruz, CA 95060

Clinical Investigator Name:

Research Site Address(es):

Daytime telephone number(s):

24-hour contact number(s):

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM
This consent form describes a research study and your role as a subject. This consent form may contain words you do not understand. Please read this form carefully before you decide to take part in this study. You may ask the study therapists anything about the information provided.

The purpose of this form is to give you information about the research study and, if signed, gives your permission to take part in the study. The form describes the purpose, procedures, benefits, risks, discomforts and precautions of the research study. You should take part in the study only if you want to do so. You may refuse to take part or withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. Please ask the study therapists to explain any words or information in this consent that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision. You should not sign this form if you have any questions that have not been answered to your satisfaction.

Your study therapist will be paid to conduct this research study.

PURPOSE AND BACKGROUND
You are being asked to take part in this research study because you have been diagnosed with posttraumatic stress disorder (PTSD) and because your symptoms have not gone away after psychotherapy, medicines or both, or you stopped your treatment because you could not tolerate it.

This small ("pilot") study is designed to provide information on whether psychotherapy ("talk therapy") combined with the drug MDMA is safe and helpful for people with posttraumatic stress disorder (PTSD). The researchers plan to use the results of this study to design further studies.

MDMA is an experimental drug, which means that it has not been approved by the Food and Drug Administration (FDA) for sale for medical use in the United States. MDMA is also a controlled drug (illegal to use outside of research) and is sometimes known as "Ecstasy" (which is supposed to contain MDMA, but often contains other drugs instead of or in addition to MDMA). MDMA has already been used legally in research and illegally in uncontrolled environments, such as nightclubs. While much is known about MDMA and its risks, much remains unknown about this drug.

The study is sponsored by a US-based non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org). MAPS' first small study of MDMA-assisted psychotherapy in 21 people with PTSD is finished in the U.S. MAPS has completed another MDMA/PTSD pilot study in Switzerland and is conducting new studies in the U.S., Canada and Israel.

Before it became illegal in 1985, some psychologists and psychiatrists combined MDMA with psychotherapy to help people with psychological problems, including PTSD. Though we do not know why it may help people with PTSD, we know that MDMA increases positive mood and changes the way we see and think about the world around us, making it easier to think about and recall things that happened to us that are upsetting. People say they feel caring and forgiving toward themselves and others during the MDMA experience. It is possible that these drug effects, when combined with psychotherapy, help people work through thoughts, memories and emotions related to PTSD.

This study will compare safety and efficacy of different doses of MDMA using one of two active doses of MDMA and a comparator dose. During experimental sessions participants will receive an active dose of MDMA or a comparator, which may have MDMA in it, possibly followed one and a half to two and a half hours later by a second dose equal to half the size of the first dose.

LENGTH OF STUDY

The length of the study depends on your group assignment to one of the active dose arms or the comparator arm. Participation in the study requires a big time commitment on your part.

- **Active Dose Arms:** This study can take up to 1.5 years or 18 visits if you are assigned to one of the active doses of MDMA in "Stage 1." This time period includes active participation for 3.5 months. After that you will come back 2 months and 12 months after the last experimental session for a last follow up visit.
- **Comparator Dose Arm:** If you receive the comparator dose in Stage 1 the study can take up to 1.8 years or 28 visits to complete both stage 1 and 2 plus the long term follow up visit. If you are in the comparator group, you will have 12 visits in stage 1 over 2.5 months. If you choose, you can have an additional 15 visits in Stage 2 where you receive the active dose MDMA over 3.5 months. This time period includes 6 months of active participation. After that you will come back 12 months after the last experimental session for a last follow up visit.

The timeline after enrollment for starting treatment can move fast or slow depending on availability of open appointments You may start therapy as soon as one week after enrollment or be delayed by as long as two months. Depending on your group, you will visit the therapist's office approximately once a week for 3.5 (active dose groups) or 6 months (comparator dose group) during the active period. Experimental sessions last all day and require an overnight stay; they are approximately once a month for 3 or 6 months depending on the group you are assigned to. After these overnight stays, you will also have a brief daily phone call with the therapists for 7 days and you will have 3 psychotherapy sessions a week apart. You will have testing visits, which require lengthy interviews, 4-5 times during the study. After active participation is complete, you will have a follow up visit two months after your final experimental session and one year later.

Types of visits and duration:

Psychotherapy sessions (90-minutes each): 3 introductory sessions at the start of participation and 3 sessions after each experimental session. These are approximately once a week.

Experimental sessions (8-hours long plus an overnight stay): 3 sessions for each person in the active dose arms and 2 sessions plus 3 optional sessions for each person in the comparator dose arm. These are approximately monthly.

Evaluation and Testing Visits (Up to 4 hours): Testing and completing questionnaires 4-5 times, starting with the beginning of the study.

You will need to be flexible and take the appointments we offer most of the time because there is a limited time frame for each type of visit and there are many participants we need to accommodate.

TYPE OF STUDY

This study is double blind, meaning that neither you nor the study researchers will know what you will get. However, in the event of an emergency this information may be obtained. The drug you get will be decided at random, as if by tossing a coin. You will have a 78% chance of receiving an active dose of MDMA and a 22% chance of receiving the comparator. You will find out what you received approximately 1 month after your second experimental session is complete. There will be 23 subjects in this study.

PROCEDURES/WHAT WILL HAPPEN TO YOU

SCREENING/EVALUATION AND BEGINNING OF STUDY

If you agree to take part in this study, you will first sign this form before any study-related procedures are performed. You are required to stay on any current medications until you are enrolled in the study, and to stop medications only if you are enrolled under the care of the study doctor. Some PTSD medications can cause thoughts about wanting to kill yourself if you stop taking them too quickly and without the care of a doctor

Before you can be in the study, the study doctor must first make sure that you qualify for the study and that you are generally physically healthy. The screening process can take up to 2 months, and there will be one or more office visits during this time. The study doctor may ask your permission to contact your doctor or psychotherapist to get information about your medical history. They may need to do this so that they will know if you can be in the study or not.

The person asking you these questions will be a study researcher other than your study therapists. The tests will include the following:

- A questionnaire about your PTSD symptoms and how you deal with them in your everyday life. Your score on this questionnaire will be used to decide if you can be in the study. This session may be recorded to video.
- Questions about your medical history, including questions about your emotional and psychiatric history. This may include any previous medical or psychiatric problems or treatment and may include questions about difficult experiences you may have had during childhood or at other times of your life. The study doctor will rate how well you are doing in general.
- Questionnaires that you fill out yourself about your PTSD symptoms.
- A questionnaire about feelings of depression or other symptoms or feelings you might experience.
- A questionnaire about thoughts or feelings you might have about hurting or killing yourself.
- A questionnaire about your quality of sleep.
- A questionnaire about any dissociation symptoms
- A questionnaire about personality traits, which may be followed by an interview to discuss the questions.
- Two different tests of attention, memory, and different types of problem solving. These are not tests of intelligence.
- A visual scale of pain and tinnitus (ringing in the ears) levels if you have these symptoms.
- A physical examination that will include measures of your blood pressure, pulse, temperature, and body weight.
- An ECG (electrocardiogram) will also be taken, which is a recording of the electrical activity of your heart.
- A sample of your blood (about 2 tablespoons) and a urine sample for routine laboratory testing, including tests of metabolism and liver function. Laboratory tests will also include testing for the human immunodeficiency virus (HIV).
- A urine test for drugs of abuse. Your urine drug screen must be negative to take part in the study.
- A urine pregnancy test if you are a woman and are able to get pregnant. Your urine pregnancy test must be negative for you to take part in the study.

If the tests find out that you test positive for HIV, we will notify you, then the study doctors will have to tell the [redacted] within seven days, as stated by law. If you live outside [redacted], the study doctors will report the results to your state health authorities. If you do not want to be tested you should not take part in this research study.

BEGINNING OF STUDY

Once you are in the study, you will schedule your first preparatory psychotherapy session with the study therapists. You will need to be enrolled in the study before receiving psychotherapy. If you were taking psychiatric medicines before enrolling in the study, you will have to stop taking them after you are enrolled in the study. The study doctors and your physician will help you do this. You must let the study therapists know about any medical conditions or procedures, like surgery, within 48 hours of their

occurrence. Your study therapists will ask you your opinion on having three experimental sessions.

You will need to give the study therapists the name and contact information (telephone number, cell phone number or email) of a relative, spouse or close friend to contact in case of medical emergency, as when you might be at risk of hurting yourself, or someone else, so they can reach that person to let them know what is going on.

SCHEDULE OF EVENTS

Time is counted from the first study visit after you are selected to be in the study. The tables below show the type of visits you will have in Stage 1 and Stage 2 (if you are in the comparator group).

Stage 1	Screening	Intro and Preparation	Therapy 1	Therapy 2	Evaluation	Therapy 3	Evaluation	Long Term Evaluation
For Both Groups						**For Active Dose Group Only**		

Study Visit #		1 Enroll	2*	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Screening	X																		
Measure symptoms	X												X					X	X
Memory/ Attention tests	x												x					x	
Psychotherapy		X	X	X		X	X	X		X	X	X			X	X	X		
Psychotherapy with drug					X				X					X					
Medical Exam	X																		
Learn what you received													X						

Stage 2	Preparation	Therapy 1	Therapy 2	Evaluation	Therapy 3	Evaluation	Long Term Evaluation
For Comparator Group Only							

Study Visit #	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
Measure symptoms	X*									X					X	X
Memory/Attention tests															x	
Psychotherapy	X		X	X	X		X	X	X			X	X	X		
Psychotherapy with MDMA		X				X					X					

* Symptoms may be measured again if more than 8 weeks passes between Visit 12 and 18.

PREPARATORY PSYCHOTHERAPY SESSIONS:
You will meet with the study therapists on three separate occasions before the first experimental session. These visits will last 90 minutes. During each introductory session, you will talk about the traumatic incidents that led to your PTSD, the ways PTSD symptoms are affecting your life and what you would like to achieve during these sessions. You will be asked the same questions about thoughts or feelings you might have about hurting or killing yourself during one of these preparatory sessions. You will also learn more about what to expect during experimental sessions. The introductory sessions will be recorded to video so that the study therapists will have accurate records of the sessions and so that they can gather more information about drug-assisted psychotherapy sessions. You can ask the study therapists to let you see these recordings if you wish.

EXPERIMENTAL SESSIONS:
There will be two day-long experimental sessions, when you will have an active dose or a comparator dose and psychotherapy, each happening three to five weeks apart. The first experimental session will occur after you have had three introductory sessions. If you are in the active dose group, you will have a third day-long experimental session with MDMA. If you received the comparator, you will be offered one of two active doses of MDMA during Stage 2 experimental sessions. Your therapists will discuss the optimal dose of MDMA with you for the second and third experimental sessions.

One week before each of the experimental sessions, you will need to avoid taking:

- any herbal supplement (except with prior permission);
- any non-prescription medications, unless you have permission (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen [Tylenol]);
- any prescription medications, unless you have permission (with the exception of birth control pills, thyroid hormones or other medications).

You must not eat any food or drink any alcohol after midnight on the night before each session, though you can drink non-alcoholic liquids during this time, such as water or juice. You cannot use any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session. You cannot use nicotine or caffeine for two hours before and six hours after drug administration.

If you are taking opiate medications for pain management, you can remain on these medications, although we may ask you to reduce the dose or avoid taking them for at least 24 hours before the experimental sessions, because these medications may reduce the effectiveness of MDMA. If your pain becomes too severe to handle during this period, you will be allowed to take your medication.

First, you and the study therapists will discuss your goals for the experimental session and the study therapists will answer any other questions you may have.

Before an experimental session:

- Your urine will be tested for drugs of abuse, including stimulants, sedatives, opiates and cannabis.
- If you are a woman who can become pregnant, you will take a urine pregnancy test.

Throughout an experimental session:

- Your blood pressure and pulse will be measured periodically (every 30 minutes).
- Your temperature will be measured every hour to every hour and a half.
- You will also complete a very brief, simple test of how comfortable or distressed you feel by marking a number on a sheet of paper that matches the way you feel at that moment. You will complete it every 60 to 90 minutes throughout each experimental session.
- About an hour before receiving the drug and about six hours afterward, you will complete the questionnaire about thoughts you might have about hurting or killing yourself.
- The study therapists will check in on you every hour or so to see how you are doing.
- If you had tinnitus or chronic pain before the study and mention any changes in these symptoms, the visual scale will be used to collect the changes.

The experimental session will be recorded to video so that the study therapists will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. You can ask to see these recordings if you wish.

After urine test results come back, you will receive a capsule containing an active dose or the comparator dose mixed with some lactose (a kind of sugar) to make all capsules appear and weigh the same. After taking the capsule, you will then sit or lie down in a comfortable position. You can ask for an eye shade if you wish. You will listen to music during much of each experimental session, either through headphones or room speakers. Periodically you will be asked to talk to the study therapists. If you are wearing headphones, you may remove them yourself if you want to talk to the study therapists or have periods of silence. Lying or sitting in a comfortable position and listening to music are meant to bring out thoughts and feelings, including thoughts and feelings about the trauma. Both study therapists will remain with you, and they will help you if you need them to do so. They will speak with you and ask you to talk to them at least once an hour, but you can talk to them whenever you wish. There may be times when the study therapists will suggest that you stop talking for a while in order to pay attention to your thoughts and feelings. There will be beverages available, including water, juices, and Gatorade® or similar sports drinks, and you will be encouraged to drink an adequate amount of fluid. You can drink it whenever you wish to do so, within the limits of the amount that is safe for your body. Later on, food will also be provided.

Approximately one and a half to two and a half hours after you took the first capsule, you and the study therapists will talk about taking a second capsule. The second dose will contain half the amount of the first capsule. If you and the study therapists agree, you will take the second capsule. If you or the study therapists notice problems after the first capsule, then you will not get the second capsule.

The study therapists will keep measuring blood pressure, pulse and temperature, and they will watch for any side effects (unwanted effects or health problems), which will be treated if they see them. If this happens, the study therapists will let you know what they are doing.

If you are confused or upset eight or more hours after the start of an experimental session, the therapists will stay with you until you have fully recovered. If the therapists think you are at risk of hurting yourself or others, they will either remain with you all night or have you admitted to a hospital until you are no longer at risk of hurting yourself or others. The therapists will ask you about thoughts of killing or harming yourself before and after drug administration and on several occasions during the phone follow-up period. You will also be asked to complete a questionnaire about thoughts, feelings or other things you might have experienced during the experimental session. You can complete this questionnaire at any time between the end of the experimental session and the time you leave the study site the next day.

If you request it and the study therapists agree to it, you can have a companion stay with you during some or all of the experimental session, starting at an agreed-upon time, or when you stay at the office of the therapists after the session. When he or she arrives, your companion will stay in the waiting room until there is a good time for them to come into the session.

You will be spending the night in a room at the office of the therapist with an attendant who will be staying in another room nearby. You can use the kitchen or walk around outside if you want. If you find you need to talk with the therapists or you are having other problems and need to contact the therapists, the attendant will contact them immediately.

On the next day, you will have a non-drug (integrative) therapy session with the study therapists. You will need to have someone drive you to wherever you are staying (home, hotel or another location) from the non-drug therapy session on the day after the experimental session because we do not know how MDMA will affect your ability to drive, and because some people report feeling tired, less alert or having trouble concentrating a day after having taken MDMA. If you cannot find anyone to take you home, the therapists will find someone to drive you.

After you return from the non-drug therapy session, the therapists will telephone you every day for a week to ask how you are feeling and determine whether you should see the study therapists before your next scheduled non-drug psychotherapy session. These telephone calls will take approximately 5 to 15 minutes, though they can be as long as you need them to be. You may schedule additional meetings with the study

therapists besides those that are scheduled as part of the study if you and/or the therapists believe they are necessary. You can contact the study therapists at any time. The study therapists will be reachable by telephone 24 hours a day throughout the research study, except on occasions when they are out of town. At those times the study doctor will be on call and can be reached through his phone number that will be given to you as well.

The therapists will give you a card with telephone numbers for reaching your study therapist and the Copernicus Group Independent Review Board (IRB), which is an independent committee that protects the rights and welfare of study participants. You can keep this card in your wallet to make it easier for you to contact the therapists if you need to do so.

If there are delays in following the usual study schedule, the study therapists will telephone you at least once a week to talk about how you're doing. These telephone calls will take approximately 15 minutes, and you agree to call the investigators if any of these things happen: you have an increase in symptoms for which you previously took medicine, you need to contact your outside therapist other than for the usual appointments, and/or you start or stop taking prescribed medicine.

If you have very high blood pressure, get sick, or have an important and strong lasting reaction (unwanted effect or health problem) during or after an experimental session, you or the study therapists may decide that you should not take part in the next experimental session. You may make this decision to stop treatment in the study for any reason.

If the study therapists decide to take you out of the study, they will let you know that they are doing this and their reason for doing this. If you are taken out of the study or decide you do not want to receive treatment in the study, the study researchers will ask you to complete some final questionnaires about your PTSD symptoms. If you decide you do not want to continue in the study during an experimental session, you will still have to stay in the office until the study therapists think that you are well enough to leave and that all the effects of the drug have worn off. If this happens, you will also be asked to take part in some of the same interview and questionnaires you completed at the beginning of the study. You will also be expected to take part in the 12-month long-term follow-up.

The next experimental session will occur three (3) to five (5) weeks later. All experimental sessions will be carried out in an identical manner to the first session.

PSYCHOTHERAPY AFTER EXPERIMENTAL SESSIONS

You will have regular psychotherapy to help you express, understand, bring together and connect any thoughts or feelings you may be having about your symptoms and their causes, and to think and talk about your experience during experimental sessions. You will have psychotherapy with the study therapists the morning of the day after each experimental session and then two more visits during the next month after each experimental session. These sessions will last 60 to 90 minutes. You and the study

therapists will also talk about ways to use what you learned to help work on treating your PTSD, face and solve difficulties you may have faced during the experimental sessions and gain maximum benefit and understanding from experimental sessions. Each regular psychotherapy session will be recorded to video, just like the introductory and experimental sessions, and you can see these recordings if you wish.

On the third session of regular psychotherapy, you will complete a questionnaire about your PTSD symptoms.

Before starting psychotherapy on the day after each experimental session, you will be asked if you believe you got MDMA. You will not be told if your guess is correct.

If you had tinnitus or chronic pain before the study and mention any changes in these symptoms, the visual analog scale will be used to collect the changes.

The researchers will ask you about thoughts about killing or harming yourself during each follow-up session, and during the second and seventh day of telephone contact with the study therapists.

MEASURING PTSD AFTER EXPERIMENTAL SESSIONS

Approximately four months after the start of the study (one month after the second experimental session), you will meet with the study researcher again. The researcher will ask about your PTSD symptoms (which may be video recorded), and you will fill out questionnaires on your PTSD symptoms, feelings of depression, sleep quality, and dissociation symptoms. You will have the same tests of attention, memory, and different types of problem solving that you had at the beginning of the study. You will also complete the scale of pain and tinnitus levels if you had these problems before the study.

The tests will help the study therapists tell if your symptoms have changed or stayed the same over time.

After you complete these tests, you will meet with the study therapists and all of you will find out if you received MDMA or the comparator. The study researcher who measured your PTSD symptoms will not find out. You will also be asked if you have had any thoughts about hurting or killing yourself.

If you learn that you had the comparator, you can then enroll in “open label” study sessions, or “Stage 2,” described below. If you decide not to take part in Stage 2, then you will complete a questionnaire about your experience as a research subject before you leave the first part of the study. You will also be expected to take part in the 12-month long-term follow-up.

If you are in the MDMA group, you will be asked about your thoughts on having a third experimental session. You will then schedule and complete your last experimental session, which will be “open label,” meaning you will receive MDMA, but this time you will know. You will have the same regular psychotherapy visits after this last experimental session.

Active Dose Group Only – Approximately six months after the start of the study (two months after the third experimental session), you will meet with the study researcher again. The researcher will ask about your PTSD symptoms (which may be video recorded), and you will fill out a questionnaire on feelings of depression, a sleep quality questionnaire, a dissociation symptoms questionnaire, and PTSD symptom questionnaires. You will complete the two tests of memory, attention, and problem solving. You will also be asked if you have had any thoughts about hurting or killing yourself. This visit should last between about 2.5 and 3.5 hours.

The tests will help the study therapists tell if your symptoms have changed or stayed the same over time.

You will complete a questionnaire about your experience as a research subject before you leave the first part of the study. You will be asked about your thoughts on having a third experimental session. The study therapists will give you a memory aid card. This card is to help you to remember any new problems or medical conditions, or changes in medication during the months between this visit and your last visit, the 12-month follow-up visit. On this card you will record any new important health problems, changes to your mental health, hospitalizations and medications to treat these problems.

OPEN-LABEL ACTIVE DOSE SESSIONS FOR PEOPLE WHO RECEIVED THE COMPARATOR (STAGE 2)

If you are one of the five subjects who received the comparator, you can take part in three open-label MDMA-assisted sessions scheduled 3 to 5 weeks apart as part of Stage 2. In this part of the study, you will receive an active dose of MDMA during each experimental session. Stage 2 can start any time after the end of Stage 1 but not later than five months after Stage 1 ends. Signing this consent form means you agree to take part in the second part of the study though you can change your mind at any time and still take part in the 12-month follow-up without taking part in Stage 2. **The 18 people who receive active doses of MDMA during the first stage of the study cannot take part in Stage 2.**

If you take part in Stage 2, you will have 15 more visits. In Stage 2, you will know you are getting an active dose of MDMA and will have three experimental sessions instead of only two. You will also only have one preparation session instead of three. You will have tests of your PTSD symptoms, depression symptoms, sleep quality, and dissociation symptoms one month after the second open-label session and two months after the third open-label session. You will complete the scale of pain and tinnitus levels if you had them before the study. You will also be asked if you had any thoughts about hurting or killing yourself during that time. You will be asked about your thoughts on having a third experimental session before and after your third session. You will complete a questionnaire about your experience as a research subject. You will complete the tests of memory, attention, and problem solving with the study researcher. After you complete the questionnaires two months after your last open-label session, the study therapists will give you a memory aid card. This card is to help you to remember any new problems or medical conditions, or changes in medication during

the months between this visit and your last visit, the 12-month follow-up visit. On this card you will record any new important health problems, changes to your mental health, hospitalizations and medications to treat these problems.

LONG-TERM FOLLOW-UP 12 MONTHS AFTER LAST EXPERIMENTAL SESSION – FOR ALL SUBJECTS

Approximately 12 months after your last MDMA-assisted session, you will answer questions about your PTSD symptoms, feelings of depression, sleep quality, and dissociation symptoms and you will fill out a questionnaire on the positive and negative effects of being in the study. If you were only in "Stage 1," then this will happen 12 months after your third experimental session, and if you were in Stage 2, then this will happen 12 months after the third open-label session.

The same study researcher who asked you about your PTSD symptoms will do so again, either in person or over the telephone. The study therapists will ask you about any changes in medications or your psychiatric health, including any benefits or harms, during the follow-up period between your last visit and the 12-month follow-up visit.

You will also answer the questionnaire about feelings of depression, your quality of life, your sleep quality, dissociation symptoms, and a PTSD symptom questionnaire. The questionnaires will include questions about any thoughts, feelings or events that happened after being in the study. You will also answer a questionnaire about your attitudes and feelings about being in the study, any thoughts you have about the good and bad points of MDMA-assisted therapy, and your thoughts about taking MDMA. There are no right or wrong answers to these questions.

The researchers will ask you about any changes in medication or your psychiatric health, including any benefits or harms, during the follow-up period between your last visit and the 12-month follow-up visit. The visual scale will be used to collect changes in tinnitus and chronic pain symptoms if you had them before the study.

The questionnaires may be mailed to you for you to fill out. If so, they will come with an envelope that is already stamped and have only the researcher's address on it. Do not put your name on the questionnaire.

The researchers will use your answers to these questionnaires to see if there are any long-lasting effects of being in the study, such as changes in PTSD symptoms or other life events. They may be able to learn what happens to people who started out receiving MDMA versus people who received the comparator first, and then received MDMA.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

POSSIBLE RISKS OR DISCOMFORTS
MDMA has not been widely tested in humans, but as of December 2015 more than 1185 people have been given MDMA in clinical research settings, without any serious unexpected problems happening. Some of the effects that have been observed are listed below.

Side effects that are most frequently reported by 25% or more of participants during the MDMA experience (100 to 125mg) are:

- Muscle tightness (jaw) (55%)
- Decreased appetite (42%)
- Muscle tightness (27%)
- Nausea (27%)
- Feeling Cold (27%)
- Sweating (25%)
- Restlessness (25%)

In these studies, participants (mostly with PTSD) also experienced anxiety, headache, and fatigue at a similar rate during MDMA or placebo. Less than 25% of participants receiving MDMA reported dizziness, insomnia, thirst, problems walking or with balance, dry mouth, difficulty concentrating, depressed mood, and nystagmus (eye wiggles), from most to least common. When these side effects occur, they usually last less than four hours. However, some effects have been reported to last for more than 24 hours and (rarely) for as long as four days.

There may be unknown side effects or risks from the use of MDMA.

Other possible risks of MDMA may include the following:

***Serious problems*:** There have been some serious problems, and even deaths, associated with the use of ecstasy outside of controlled clinical or laboratory settings. These problems have included high fever, brain swelling associated with drinking too much liquid, convulsions, and liver damage. Some recreational users of ecstasy have become severely anxious, depressed or paranoid (thinking that other people are out to get them). Since you will be receiving moderate amounts of uncontaminated MDMA in a controlled setting with trained therapists who will be closely monitoring your physical and psychological reactions, these problems are not expected to occur either during or after the experimental session. While this does not guarantee that they will not occur, it does mean that if they do occur, the study doctors are prepared to respond in a safe and professional manner.

***Changes in vision, hearing or other senses*:** In previous studies in which MDMA was given to volunteers (including a total of about 365 participants without emotional disorders and 21 with PTSD) most participants reported experiencing temporary and minor changes in vision and hearing, such as sounds seeming closer or farther away than usual or objects seeming brighter than usual. These changes typically lasted 2 to 3 hours. People also reported unusual feelings in their bodies, such as tingling or numbness (between 12% and 33%).

***Blood pressure and heart rate*:** The effects of MDMA usually last 4 to 6 hours. At the dose in this experiment, the increases in blood pressure and heart rate are likely to be moderate. Average increase in systolic blood pressure is 28 mmHg (measurement unit for blood pressure) and average diastolic blood pressure increase is 13 mmHg. Heart rate may increase by approximately 30 beats per minute (BPM) on average.

In previous studies, blood pressure rose well above normal levels in a few subjects (a little less than 5%) after receiving MDMA, but these subjects did not report any discomfort and did not require any treatment. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in individuals with pre-existing heart or vessel conditions. These serious problems could include an irregular heartbeat heart attack or stroke. We will screen all potential subjects for preexisting heart problems before they are allowed to be in this study. While this doesn't guarantee that no heart problems will occur, it does reduce the risk of this happening.

***Anxious or jittery feeling*:** Some participants in past studies with an anxiety disorder who received MDMA (48%) or placebo (58%) reported feeling over-stimulated or anxious at a similar rate. These feelings usually lasted less than 30 minutes. Letting yourself accept and feel these emotions deeply can be part of the psychotherapy. If you are not able to deal with these experiences in a way that helps you, the study doctors will work with you to deal with these feelings. It is possible that if such periods of heightened emotion do not clear up or grow weaker during the session, you could be at increased risk for suicide or other self-harm afterwards. You will be encouraged to ask the attendant to call the study therapists immediately if you have any thoughts about hurting or killing yourself so they can help you resolve them safely. If necessary, they may prescribe anti-anxiety medication or medication for sleep.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the researchers may require you to be admitted to a hospital.

***Insomnia & Drowsiness*:** In previous studies, between 7% and 23% of subjects have reported insomnia (difficulty sleeping) or feeling tired, irritable, or drowsy for as long as 3 days after receiving MDMA. If needed, the study doctor may prescribe medication for sleep. **You should not drive or use machinery immediately after each experimental session (up to 24 hours afterwards).** This is because the study drug may cause drowsiness, lack of coordination or slower reaction time.

***Mood*:** Some after-effects of MDMA may be noticeable up to 2 or 3 days later. While some subjects feel that their mood is better, 11% feel that it is worse.

***Immune System*:** You may have a less active immune system for 2 or 3 days after receiving MDMA. This may make you more likely to become sick with a cold or other infection during this time. The study describing this finding did not report how many people in the study showed these changes.

***Addiction*:** There is a small chance that you will become dependent on (addicted to) MDMA. One study found that up to 6% of people using ecstasy for recreational purposes were dependent on it. However, a study of people who had received MDMA for the first time in a legal laboratory setting found that they did not want to try MDMA again outside of the laboratory.

People who have recently (in the last 2 months) had problems with drug abuse should not take part in this study.

Possible Brain Damage: Experiments in rats and monkeys show that high and repeated doses of MDMA can change certain brain cells that release a chemical called serotonin; in mice (though not in humans), the affected cells release dopamine. The changes include loss of the parts of the cell (called “axons”) that connect different brain areas. Rodents given repeated, high doses of MDMA are less sensitive to a later dose of MDMA, are more likely to become overheated when placed in a warm room, and some studies find they perform worse in difficult memory tests. Recent studies in monkeys and rodents suggest that the doses used in these studies are far higher than those typically taken by humans in either recreational or laboratory settings.

Many studies found that people who had used ecstasy many times in recreational contexts were not able to recall words, pictures or patterns as well as people who did not use ecstasy, and performed less well on tests of planning and impulse control. These differences are not great, but they have lasted for at least a year after people had stopped taking ecstasy. Not all studies have found ecstasy users to have difficulty recalling words or pictures or to have impulse control problems. When compared with people who do not use ecstasy, studies found Ecstasy users were more likely to report feeling generally anxious or depressed. Many of these studies found that using alcohol or other drugs was also associated with feeling anxious or depressed. At least two studies found that people who are anxious, depressed or have psychological problems before taking any drugs are more likely to take ecstasy than people without these problems, but there is no proof that MDMA might not cause these problems in some people.

Only one study has looked at brain scans of people before they got MDMA and then again after they have received one or two moderate doses of MDMA. This study did not show any changes in the brain following MDMA, though it is possible that there were changes that were too small to notice. Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and found one small change in the amount of blood flow in a specific part of the brain, but did not show signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area. Findings from these studies suggest that the amount of MDMA you will receive in this study will not produce any lasting changes in your brain, though this is not guaranteed.

Studies of people receiving one or two doses of MDMA in a laboratory setting have not found any lasting changes in memory or planning. Studies comparing people before and after they decided to take a few tablets of ecstasy in a recreational setting with people

who did not take them found less improvement in memory in the people who took ecstasy, and no other changes in thinking or planning. It is believed that the amount of MDMA you will receive will not produce any lasting changes in memory or planning, though this cannot be guaranteed.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the study therapists may require you to stay in a hospital.

Risks of Being in the Study:
If you are tested for drugs of abuse within three days of each experimental session, you may test positive. The study therapists will provide you with an information card in case you are tested for drugs of abuse, and if you are tested for drugs of abuse while you are in this study, you can have the person(s) testing you call your study therapist to verify that you are in this study.

The interviews you have during the study involve no specific risks or discomforts beyond those of a standard clinical interview situation. You may feel upset at the review of your emotional experiences, or you may feel boredom or fatigue. Answering questions about thoughts you might have of hurting or killing yourself may be upsetting.

The medical evaluation involves some blood tests. The risks of blood drawing include temporary discomfort from the needle stick, bruising and, rarely, infection at the site of the needle stick. Fainting could also happen.

It is possible that after you stop taking psychiatric medicine (as for depression or anxiety) as part of the study, you may start to have symptoms again. There is also a risk that you may have thoughts of hurting or killing yourself when you stop taking medicine, especially if you have had these thoughts before. If this happens, you should talk with your outside therapist and your study therapist. If you have to start taking medicine again, then the study doctors will have to take you out of the study.

REPRODUCTIVE RISKS
Effects of MDMA on the growth and development of an unborn baby are not known; therefore, you will not be allowed to enter the study if you are pregnant. If you become pregnant after you have had at least one experimental session, the study doctors and the sponsor (MAPS) will ask you about and keep track of the pregnancy and will need to know about the outcome of your pregnancy.

Women who are able to become pregnant must use one of the allowed birth control methods, such as birth-control pills or shots, IUDs, and diaphragms used along with spermicide and with partner use of condoms until after the final 2-month follow-up assessment and for at least one month afterward. The study therapists will explain these methods to you and will help you decide which might be best for you, and they can suggest to you where you can get more information and advice.

If you are a woman of childbearing potential, you will be tested at the start of the study and again before each experimental session to see if you are pregnant. If, at any time during the study, you think that you may be pregnant or are worried that you may become pregnant, you must notify your study therapist immediately. If you should become pregnant during the study, the study doctors will help you get proper advice and help you and your unborn baby get proper care while you are pregnant.

NEW FINDINGS
If any new information becomes available about MDMA while you are taking part in this study, the study therapists will tell you about it as soon as possible. You may contact the study therapist at any time after your participation ends to find out if any new information about this study has become available.

POSSIBLE BENEFITS
Your symptoms of PTSD may improve while taking part in this study. There is no guarantee that you will benefit from taking part in this research study. Information obtained from this study may help doctors and researchers to improve treatment for PTSD in the future.

PAYMENT FOR PARTICIPATION
There will be no payment for taking part in this study.

[redacted]

COSTS
The sponsor of this study, MAPS, will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions that are a part of this study, for the psychological and laboratory testing, for medical examinations, including any extra tests you might have, solely to see if you can be in the study (if you are eligible) and for the study drug. You, your private medical insurance (if any), or public health insurance plan will not be charged for any procedures done solely for the purpose of the study. You or your insurance company will remain responsible for on-going treatment unrelated to the study.

This is a local study and travel costs may not be covered. An alternative is that you could pay for your own travel costs to participate in the study.

ALTERNATIVES
One alternative to being in this study is to decide not to take part. You may decide to try other treatments for PTSD. There are other medicines, such as Paxil (paroxetine) or Zoloft (sertraline) and anti-anxiety medications such as Xanax (alprazolam) and other forms of psychotherapy that you could try. If you are currently having psychotherapy and/or taking medicine, you could continue with those for a longer period of time. The study therapist can discuss the alternatives and their potential risks and benefits with you.

CONFIDENTIALITY
To ensure confidentiality, your information will be stored in secure electronic systems or in a locked office. Absolute confidentiality and security cannot be guaranteed, but every effort will be made to maintain your confidentiality.

People outside of your treatment team will need access to your information to monitor the study and conduct further research and training. Any paperwork copied will have any information that could be used to identify you removed first, except for videos, which will still show your face. If records are copied, only your participant number and initials will identify you to the study sponsor unless you give specific permission, for example at a time when you sign a media release.

Medical records, including video, which identify you, and the consent form signed by you will be looked at and/or copied for research or regulatory purposes. These records may be looked at by:

- The sponsor, MAPS and the people they hire.
- Researchers who cooperate with MAPS to conduct further research, and people who conduct therapist trainings on behalf of MAPS.
- The FDA and similar agencies in other countries.
- Governmental agencies in other countries.
- The Copernicus Group Independent Review Board (CGIRB).

All records in [redacted] are subject to subpoena by a court of law.

The results of this research study may be presented in meetings, presentations, or in publications, where your identity will not be disclosed. Video of your sessions may be used in training sessions for research therapists or other researchers only in controlled settings as described below.

Video recordings: The study therapists will video record each visit. The purposes for this recording that you are agreeing to by signing this informed consent are:

- So that you will have access to review your own therapy sessions.
- So the study therapists will have accurate records of the session.
- So that trained raters working for the sponsor can verify that the therapy is being carried out according to the protocol and the methods described in the Treatment Manual, or for further development of the Treatment Manual.
- For further research on the therapy and how it is performed.
- For training other therapists and scientists to develop and work on additional research.

For the above purposes the adherence raters, researchers and therapists who may be viewing these recordings will be selected by the sponsor, and will sign confidentiality agreements to ensure they do not share the identifying information they may receive.

Information contained in recordings that could be used to identify you may include:

- Your physical appearance
- Your voice
- Your name (if it is spoken on the recording)
- Situations from your life that might be discussed

You may watch the recordings if you wish, but you do not have to. Due to processing time required, they will not be available immediately after your visit. Once the recordings are processed you may request access to your own recordings. Your name or other identifying information will not be used to label these recordings. Sometimes audio or transcripts from these video files will be processed separately and used for additional research.

With your permission, the investigators and/or sponsor may use portions of your videos to educate a broader audience at medical conferences or other settings. In these settings the audience will not be specifically screened and selected, and confidentiality agreements will not be obtained from the audiences. You are not required to agree to use of your video in these settings in order to participate in the study. Signing this consent form does not mean you have given permission for your videos to be used in this way. You will have the opportunity to sign an additional release for these situations if they arise and if you choose to allow this use. At the end of the treatment period when you have completed all of the questionnaires and measures, you can make a decision about whether or not you wish to grant this additional consent.

These recordings will be stored on hard drives stored in a locked and secure location when not in use. No personally identifying information will be used to label the video recordings. A copy will be transferred to the sponsor for electronic storage on the web to allow for viewing purposes described above. Electronic systems used will include measures to protect confidentiality of your identity and video data. Total security cannot be guaranteed, but the sponsor is consistently working to maintain and improve the security of its data systems. Your videos may be viewed in online trainings or in-person trainings with pre-screened therapists. People viewing these videos will be required to sign a confidentiality agreement.

During your study sessions you may ask to stop the recording at any time, but your therapists will ask your permission to turn it back on when you are ready.

By signing this consent form, you consent to the collection, access, use and sharing of your information as described above. You have the right to check your study records and ask for changes if the information is not correct.

TREATMENT AND COMPENSATION FOR INJURY

In the event of a study-related injury, the physician who treats you will bill your insurance company. If your insurance company denies coverage or insurance is not available, then MAPS will pay for any costs that arise from treating a study-related injury, including hospitalization. Neither the sponsor nor the study therapist has a program in place to provide additional compensation in the event of an injury.

Your health insurance may not be willing to pay for the costs of treating a study-related emergency. The study sponsor will pay for any study-related procedure that your insurance will not cover.

LEGAL RIGHTS
The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this form.

VOLUNTARY PARTICIPATION
Your decision to take part in this research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to take part.

In addition, you may withdraw from (leave, stop being in) the study at any time. There will be no penalty if you decide to withdraw from the research study. Before withdrawing from this study, notify your study doctor that you wish to withdraw. This notice will allow your study doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the office for tests.

WITHDRAWAL
Your study therapist, the sponsor company, or the FDA has the right to stop your participation in the study at any time, with or without your consent, for any of the following reasons: if you have an adverse effect from the study drugs, if you need a treatment not allowed in this study, such as restarting medication for depression or anxiety, if you do not keep appointments, if you do not take the study drug as instructed, if you become pregnant, or if the study is canceled by the FDA or the sponsor company.

CONTACT FOR QUESTIONS
If you have any questions or concerns about your participation in this research study or if you feel that you have experienced a research-related injury or reaction to the study drug, or have a complaint about the research study, contact:

Investigator Name:

Daytime Telephone Number(s):

24-hour Contact Number(s):

If you have any questions or concerns about your rights as a research subject or want to discuss a problem, get information or offer input, you may contact Copernicus Group Independent Review Board (IRB) at 1-888-303-2224 (toll free). An IRB is a group of scientific and non-scientific individuals who perform the initial and ongoing ethical review of the research study with the study subject's rights and welfare in mind. Copernicus Group IRB has reviewed and approved the research study described in this form. If you have study-related comments, complaints or concerns, you should first contact the study investigator. Please call the IRB if you want to talk to someone other than the study investigator or have difficulty reaching the study investigator. For further information regarding the clinical trials process and your role as a research subject, you may visit the Copernicus Group IRB website at www.cgirb.com.

The researchers will give you a wallet card containing contact information for the researchers, the sponsor and the Copernicus Group IRB.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

SUBJECT'S STATEMENT OF CONSENT

"A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)"

My participation in this study is voluntary. I may refuse to take part in or I may stop taking part in this study at any time. I will call the researchers if I decide to do this. My decision will not affect my current or future regular medical care or any benefits to which I am entitled at this site. The researchers and/or the sponsor may stop my participation in this study at any time without my consent if they decide it is in my best interest or if I do not follow the researchers' instructions.

I agree to have my sessions video recorded during this study.

I have read the information in this consent form and it has been discussed with me. I have been given sufficient opportunity to consider whether to take part in this study. All of my questions so far about the study and my participation in it have been answered. I freely consent to take part in this research study.

By signing this consent form, I have not waived any of the legal rights which I otherwise would have as a subject in a research study. I have been told that I will be given a copy of this consent form after it has been signed and dated as well as a copy of the Experimental Subject's Bill of Rights. ***For CA Sites Only***.

_____

Signature of Subject Date

_____

Printed Name of Subject

I certify that the information provided was given in language that was understandable to the subject.

_____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

HIPAA AUTHORIZATION

The United States government has issued a privacy rule to protect the privacy rights of patients. This rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your personal health information. The document you are reading, called an "Authorization," describes your rights and explains how your health information will be used and disclosed (shared).

In working with the sponsor, the study [redacted] will use and share personal health information about you. This is information about your health that also includes your name, address, telephone number or other facts that could identify the health information as yours. This includes information in your medical record and information created or collected during the study. This information may include your medical history, physical exam and laboratory test results. Some of these tests may have been done as part of your regular care. The study doctor will use this information about you to complete this research.

In most cases, the study doctor will use your initials and assign a code number to your information that is shared with the sponsor. The sponsor and its representatives may review or copy your personal health information at the study site. Regulatory authorities and the Copernicus Group Independent Review Board may also review or copy your information to make sure that the study is done properly or for other purposes required by law.

By signing this Authorization, you allow the study doctor to use your personal health information to carry out and evaluate this study. You also allow the study doctor to share your personal health information with:

- the sponsor and its representatives
- the Copernicus Group Independent Review Board
- the U.S. Food and Drug Administration (FDA)
- other regulatory agencies

Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, these groups are committed to keeping your personal health information confidential.

You have the right to see and get a copy of your records related to the study for as long as the study doctor has this information. However, by signing this Authorization, you agree that you might not be able to review or receive some of your records related to the study until after the study has been completed.

You may choose to withdraw this Authorization at any time, but you must notify the study doctor in writing. Send your written withdrawal notice to the address on page one of this form below: [redacted]

[redacted]

If you withdraw from the study and withdraw your Authorization, no new information will be collected for study purposes unless the information concerns an adverse event (a bad effect) related to the study. If an adverse event occurs, your entire medical record may be reviewed.

All information that has already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

If you withdraw from the study but do not withdraw your Authorization, new personal health information may be collected until this study ends.

This Authorization does not have an expiration date. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely.

This Authorization will expire December 31, 2060, unless you withdraw it in writing before then. (FOR CA, DE, IL, IN, WA, WI SITES)*** ***SPONSOR USE ONLY DOC GEN PLEASE DELETE***

Your study doctor will keep this Authorization for at least 6 years. INTERNAL NOTE FOR DOC GEN **HIPAA EXPIRATION WORDING BOOKMARK**

If you do not sign this Authorization, you cannot participate in this research study. If you withdraw this Authorization in the future, you will no longer be able to participate in this study. Your decision to withdraw your

Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

AUTHORIZATION

I authorize the release of my medical records and personal health information related to this study to the sponsor and its representatives, the Copernicus Group Independent Review Board, the FDA, and other regulatory agencies as described above. I have been told that I will receive a signed and dated copy of this Authorization for my records.

_____

Printed Name of Subject

_____ _____

Signature of Subject Date

_____

Printed Name of Person Obtaining Authorization

_____ _____

Signature of Person Obtaining Authorization Date