Participant Name: _____ Date:_____

Title of Study: MDMA-Assisted Psychotherapy for Combat Veterans with Treatment-Refractory PTSD.

Principal Investigator: Shannon Remick, MD Co-Principal Investigator: Allie Kaigle, PharmD, BCPP

VA Facility: VA Loma Linda Healthcare System .

CALIFORNIA EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in an experimental clinical procedure. Before you decide whether you want to participate in the experimental procedure, you have a right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any are available to the subject after the experiment, if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of any signed and dated written consent form used in relation to the experiment.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

I have carefully read the information contained above in the "California Experimental Subject's Bill of Rights" and I understand fully my rights as a potential subject in a medical experiment involving people as subjects.

_____ _____

Date Participant Signature

LAY TITLE: ***A research study to see if adding the drug MDMA to talk therapy for PTSD helps combat Veterans who are not experiencing improvement in their symptoms with their current treatment***

KEY INFORMATION

This form uses words such as treatment, drug, medication and participant. Please keep in mind that this is a research study and the use of these terms does not mean that the use of the drug, MDMA, has been found to be effective for your condition. Before you decide whether or not to take part in this study, you should think about how the tests and study visits will affect your time away from work and your schedule.

Read this form carefully and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. You should not sign this form if you have any questions that have not been answered to your satisfaction. If you decide to take part, your signature on this form will show that you received this document, and that you were able to discuss any questions and concerns you had with a member of the study team.

WHAT IS THIS STUDY ABOUT AND WHY ARE WE DOING IT?

This research study is being done to find out if the drug 3,4-methylenedioxymethamphetamine (MDMA) is helpful in treating symptoms of PTSD when combined with psychotherapy in combat-Veterans who have difficult-to-treat PTSD. Throughout this document, MDMA may also be referred to as “study drug.” For this study, ‘treatment-resistant’ or ‘difficult-to-treat’ means that at least two preferred treatment options have failed to adequately treat your symptoms. At least one of these treatments is pharmacotherapy (medication).

MDMA is an experimental drug, which means 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 Schedule I drug (illegal to use outside of research) and is sometimes referred to as “Ecstasy” (a substance people claim contains MDMA, but often contains other drugs instead of or in addition to MDMA). MDMA is a chemical that is structurally similar to some stimulant-type drugs, like methamphetamine, which is both a major drug of abuse and an FDA-approved treatment for Attention Deficit Disorder. MDMA has 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.

This study is being funded by the VA Loma Linda Healthcare System and it is only happening at this facility. Although the study is sponsored by VA Loma Linda Healthcare System, some aspects of the study design, therapist training and drug handling procedures will be in collaboration with a

U.S.-based non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org). MAPS has completed six studies of MDMA-assisted psychotherapy in the U.S.A., Canada and Israel.

This study is open-label, meaning that you will definitely receive MDMA as part of this study, and both you and the study team will know. There is no chance that you will receive placebo in this study. A placebo is a pill that looks like the study drug but has no active ingredients; also known as a "sugar pill." Up to 50 Veterans will be asked to take part in this study, with the expectation that at least 10 Veterans will complete all visits.

WHAT DOES THE STUDY INVOLVE AND HOW LONG WILL IT LAST?

During this study, you will be asked to come to the VA Loma Linda Healthcare System for approximately 17 in-person visits, which includes three 8-hour visits with overnight stays, in addition to having several follow-up visits by telephone for the study. During the study visits, the study doctors and their research team will look at your records, ask you questions about your health, perform tests (blood samples, physical examinations and EKG, for example), ask you to complete questionnaires and interview you about your symptoms and experiences to see if this study is right for you.

Taking part in this study requires a large time commitment from you with several visits over the active study period. Although the active study period is only 19-38 weeks, we would like to follow your well-being for one year after the active study period ends. This would mean you would be in the research study for 16 to 21 months (depending on how long it takes to determine your eligibility for the study).

Although some of the activities at these visits are "usual care," which are procedures, tests or interventions that a provider would do you even if you were not in this study (such as lab draw, physical examination or therapy sessions), they are only being done as outlined in this form because you are in a research study. The "usual care" activities will be any regular visits that you have scheduled, that are not part of research.

A detailed description of the activities and procedure for this study can be found on pages 6-11 of this document.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER (OR NOT VOLUNTEER) FOR THIS STUDY?

Before you decide if you want to take part in the study, it is important that you understand:

- Why the study is being done
- The possible harms and benefits

- What you will have to do if you take part.

Deciding if you want to take part is called giving your 'informed consent.' The information in this document will help you decide. Please take your time to read the information carefully. You may wish to talk to your doctor, study staff, family or friends before deciding. Please ask the study staff if there is anything that is not clear or if you would like more information.

If you decide to take part in the study, you will be asked to sign this consent form. If you decide not to take part, your current and future medical care will not be affected.

Reason(s) a person may want to volunteer to take part in this study:

- People who take part are helping the researchers get answers about whether the study drug is safe and effective in treating symptoms of PTSD when combined with psychotherapy in combat-Veterans who have difficult-to-treat PTSD.

Reason(s) a person may not want to take part in this study:

- The length of participation and frequency of study visits may be inconvenient.
- The interviews you have during the study may cause you to feel upset.
- Like all medications, the study drug may have side effects, including allergic reaction and those that are not yet known. The most common side effects of the study drug are teeth grinding or tight jaw muscles, lack of appetite, dizziness, sensitivity to cold, muscle tension, difficulty balancing or walking, dry mouth.
- If you are tested for drugs within three days of each Experimental Session, you may test positive.
- Having blood draws and other health assessments (height, weight, blood pressure, pulse, physical exam, EKG) during the study may be uncomfortable or inconvenient.
- You cannot take part in this study if you are in another study that is testing a medicine or treatment.
- For a complete description of risks, please see pages 12-17 in this document.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer. You do not have to take part in this study to receive treatment for your PTSD symptoms; there are approved medications and psychotherapies available that the study team or your regular providers can discuss with you.

For a complete description of alternate treatments or procedures, please see page 17.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The people in charge of the study are Shannon Remick, MD and Allie Kaigle, PharmD, BCPP of the VA Loma Linda Healthcare System. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study their contact information is:

- Dr. Shannon Remick or Allie Kaigle, PharmD, BCPP at (909) 583-6361 during the day on weekdays

For after hours or weekends call:

- Dr. Shannon Remick at 909-330-6464
- Allie Kaigle, PharmD, BCPP at 909-787-4814

If you wish to contact an impartial third party not associated with this study or have questions or concerns about the research or your rights as a research subject, you may contact the Administrative Officer, Office of Research Administration, VA Loma Linda Healthcare System, 11201 Benton Street, Loma Linda CA 92357, telephone (909) 825-7084 x6050.

DESCRIPTION OF THE RESEARCH

1. WHAT IS THE PURPOSE OF THIS STUDY AND HOW LONG IT WILL LAST?

Before a new medicine can be prescribed by a doctor, it must be tested. This is to see if it is safe and if it works as it is expected to. This is called a research study. You have been asked to take part in a research study because you have been diagnosed with combat-related posttraumatic stress disorder (PTSD) that has not improved with your current treatment after at least six months of trying.

The purpose of this research is to gather information on the safety and effectiveness of MDMA combined with psychotherapy for reducing symptoms in combat Veterans who have difficult-to-treat PTSD.

Before MDMA became illegal in 1985, some psychologists and psychiatrists combined it with psychotherapy to help with psychological problems or challenges, including PTSD and couple's therapy. Though we do not know exactly why it may help people with PTSD, we know that MDMA may increase positive mood and it changes the way we see and think about the world around us, making it easier to think about and remember things that happened to us that are upsetting. People say they feel caring and forgiving towards 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 and other past experiences.

Types of preferred medications used for treating PTSD are SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors); SSRIs and SNRIs are medications that help with mood; each type works differently in the body and you could be taking (or have previously taken) one or both types already as part of your regular care.

You are being invited to take part in this study because your symptoms have not improved with the preferred treatments such as trying at least two of the following treatment options:

1. You have taken an SSRI or SNRI drug at an appropriate dose for at least 12 weeks
2. You have taken a second SSRI or SNRI at an appropriate dose for at least 12 weeks, or
3. You have completed PTSD psychotherapy sessions for an appropriate amount of time

This research study is expected to take approximately 3 years to complete. Your individual participation in this research study will be up to 21 months.

2. WHAT IS INVOLVED IF YOU TAKE PART IN THE STUDY?

If you decide to take part in this study, you will be asked to sign this consent form and will then undergo some activities and evaluations to determine if this study is a good fit for you.

The following visits and activities are expected to take place during participation:

Screening Visits (60-120 minutes each). Screening will take up to six weeks to complete and will include multiple visits to the study site and phone calls from the study team. During these screening visits, the study team will review your physical and psychological health record with you and ask you to complete some questionnaires about your symptoms and experiences. During the screening period, the following will take place:

- Your medications will be reviewed and you may be instructed to stop taking some of them once you are enrolled in the study. The study team will work with your regular doctors to make sure this is done safely. Do not stop any medications unless the study doctor gives you specific instructions on how to stop. Some medications for PTSD can cause thoughts about wanting to harm yourself if you stop taking them too quickly and without the care of a doctor. This is very important.
- The study team may ask you to sign a form that gives them permission to contact any non-VA doctors or psychotherapists to get information about your medical history. It is important that all of your health care needs be considered before giving you study drug.
- Psychological and medical screening tests will be done by the research team, which may include doctors, psychiatrists, psychologists, licensed clinical social workers, a pharmacist and research nurses/assistants. These tests will include the following:

- 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 your lifetime.
- Interviews and Questionnaires about
  - any psychological or psychiatric issues you may be currently experiencing or have experienced in the past
  - thoughts you might have about hurting or killing yourself (this will be asked at all visits and phone calls)

  Some or all of these interviews may be recorded for training and reliability purposes (to ensure the interviewers are consistently getting the same results across different interviews). Only the VA study team and training personnel at MAPS will have access to these recordings.
- A physical examination that will include measures of your blood pressure, pulse, temperature and body weight.
- An ECG (electrocardiogram), which records the electrical activity of your heart
- A sample of your blood (about 2 tablespoons) for routine lab testing, including tests of metabolism, liver function and alcohol use. All blood and urine samples will be tested in the VA Loma Linda Healthcare System laboratory.
- A test for human immunodeficiency virus (HIV) and Hepatitis C (HCV). If you have a positive test result for HIV or HCV, we will notify you. If the HIV or HCV test is positive, you cannot take part in this research study. If you do not want to be tested, you should not take part in this study.
- A urine test for routine lab testing and to test for drugs of abuse. Urine drug screening will be reviewed in order for you to take part in the study. You will not be able to take part if you are currently using or have recently used drugs of abuse. If you screen positive for drugs of abuse, we will not report findings to any authorities or employers. You will be offered a referral for substance abuse treatment, if needed, and your participation in the study will end.
- If you are female, a urine pregnancy test will be done. This test must be negative for you to take part in the study.

If you meet all of the requirements for the screening part of the study and choose to continue, you will then be scheduled for the first "Preparatory" visit. We will not know if the study is appropriate for you until we have completed the preparatory visits.

Evaluation and Testing Visits: Testing and completing questionnaires will take place at the beginning of the study, before every study drug session, and at the end of the study. After the preparatory sessions (therapy visits), you will have one of these face-to-face visits with a researcher who will ask you questions about your PTSD symptoms. This information will be used to learn how you are doing after the study treatment. After this face-to-face meeting, the study staff will let you know if you will continue on to the next part of the study.

Three "Preparatory" Visits. These visits are psychotherapy sessions with the study team. You will need to be enrolled in the study before these psychotherapy sessions can take place. If you were taking psychiatric medications before enrolling in the study, you will stop taking them at this point of the study. The study doctors, pharmacist and your regular doctor will help you do this. You must let the study team know about any change in medication, medical conditions or procedures, like surgery, within 48 hours of it happening.

You will be asked to give the name and contact information (telephone/cell phone number) of a relative, spouse or close friend to contact in case of medical emergency, if you become at risk of hurting yourself or someone else, or if the study team cannot get in touch with you. The study team will only use this number to reach out and let them know what is going on in an emergency or find out if you are okay.

The Preparatory Visits will last approximately 90 minutes. During each of these sessions, you will complete psychological questionnaires and you will talk about:

- the traumatic incidents that led to your PTSD
- the ways PTSD symptoms are affecting your life
- what you would like to achieve during the study
- thoughts or feelings you might have about hurting or killing yourself
- what to expect during the Experimental Sessions, including thoughts or feelings about taking the study drug

Experimental Sessions (about 8 hours long, and you will stay overnight at VA Loma Linda the night of each Experimental Session). After you have had the three Preparatory Sessions, you may continue to the Experimental Session part of the study. There will be three Experimental Sessions with overnight stays. The first thing that will happen at these visits is you and the study team will

discuss your goals for the Experimental Sessions and the study team will answer any questions you may have. To prepare for the Experimental Sessions, the following is expected:

- You must not eat any food or drink any alcohol after midnight on the night before each session. You can, however, drink non-alcoholic liquids during this time, such as water or juice.
- You cannot use any psychoactive drug, except caffeine or nicotine, within 24 hours of each session. This could be longer depending on the specific drug. The study team will discuss this with you, if needed.
- You cannot use caffeine or nicotine for two hours before and six hours after you take the first dose during the sessions. You will be at the study site during this time and the study team can help you keep track.
- For one week before each session, you cannot take any herbal supplements, nonprescription medications, or prescription medications that have not been discussed and approved with the study doctor.

The morning of your Experimental Sessions:

- Your urine will be tested for drugs of abuse, including stimulants, sedatives, opioids, barbiturates, PCP, and cannabis. You will also have a breathalyzer test to check your blood alcohol level. If your urine or blood results are positive for any drug that may negatively interact with the study drug, your participation will not continue. This is for your safety.
- If you can become pregnant, you will take a urine pregnancy test.
- You will be asked to answer questions about thoughts you might have about hurting or killing yourself.

During the Experimental Sessions, after the urine testing and alcohol breathalyzer is complete, you will receive capsules of MDMA as follows:

- Experimental Session 1: An initial dose of 80 milligrams (2 capsules) of MDMA. One and a half to two hours later, you will receive an additional 40 milligram dose (1 capsule).
- Experimental Sessions 2 and 3: An initial dose of 120 milligrams (3 capsules) of MDMA. One and a half to two hours later, you will receive an additional 40 milligram dose (one capsule).

After taking the first capsules, you will then site or lay down in a comfortable position. You can ask for an eyeshade if you wish. You will listen to music during much of the Experimental Session,

either through headphones or room speakers. During the sessions, there will be times when you will be asked to talk to the study team. If you are wearing headphones, you may remove them if you want to talk to the study team or have times of silence. Laying or sitting in a comfortable position and listening to music are meant to bring out thoughts and feelings, including thoughts and feelings about past traumatic experiences. The study team will remain with you, and they will help you if you need them to. They will speak with you and ask you to talk to them at least once per hour, but you can talk to them whenever you wish.

There may be times when the study team 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 juices or sports drinks (such as Gatorade®), and you will be encouraged to drink adequate amounts 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, food will also be provided.

Approximately two hours after you take the first dose, you may take a second dose. The second dose will contain half the amount of the drug of the first dose. The thought behind taking the second dose is that it is supposed to make the session last longer. If you or the study team notice you have problems after the first dose, then you will not get the second dose.

The study team will watch for any effects from the study drug that may need additional treatment. If this happens, the study team will keep you fully informed about any concerns or treatment. Your blood pressure, temperature, and pulse will be measured before taking the first and second doses and again at the end of each session. If you have any symptoms, including confusion, lightheadedness, dizziness, chest pain or shortness of breath, tell the study team. More frequent measurements may be needed if this happens.

The immediate effects of the study drug are expected to last between four to six hours, however, the Experimental Session will last approximately 8 hours. If you are confused or upset, the study team will continue stay with you until you have fully recovered. If the study team thinks you are at risk of hurting yourself or others, they will either remain with you all night or have you admitted to the hospital until you are no longer at risk. The study team will ask how you feel at the beginning and end of the Experimental Sessions and several times during the follow-up period.

Risks and discomforts are explained on pages 12-17.

You will be spending the night in a room at the VA Loma Linda facility. An attendant will be sting in another room nearby and will arrange for your dinner. You can use the amenities available or walk around outside if you want. If you find you need to talk with the study team or you are having other problems and need to contact the study team/doctor, the attendant will contact them immediately.

Integration Visits (9 total, about 90 minutes each): The day after the Experimental Session, you will have a non-drug therapy session with the study team. You will need to have someone drive

you from this session because we do not know how the study drug will affect your ability to drive. Some people report feeling tired, less alert, or having trouble concentrating a day after having taken MDMA. If you do not have anyone to take you home, the study team will assist you in finding a method of transportation. There will be two more of these Integration Visits (separated about one week apart) in between each Experimental Session.

These Integration Visits will 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 the Experimental Session. You will be asked to complete a psychological questionnaire at each of these visits.

Telephone Contacts (5-15 minutes each): When you return home from the non-drug therapy session after each Experimental Session, the study team will talk to you by phone on four days out of the following week to ask how you are feeling. If you need additional support, the study team will determine if you should be seen in person again before your next scheduled non-drug psychotherapy session. You and the study team can decide which days would be best to speak on the phone.

A member of the study team will be available to you at any time (24 hours) at the number(s) provided on page 23 of this consent form.

The study team will give you a card with phone numbers for calling the study team and the Institutional Review Board (IRB), which is an independent committee that protects the rights and welfare of study participants. We recommend you keep the card in your wallet to make it easier to contact the study team if you need to.

Measuring PTSD After Sessions (60-90 minutes): About two months after your last Experimental Session, you will meet with the study team to fill out the same questionnaires that you completed at the start of the study. You will also have the same face-to-face interview about your PTSD symptoms. The study team will measure your blood pressure and weight during this follow-up visit. These tests will help the study team tell if your symptoms have changed or stayed the same over time.

Long Term Follow Up Visit (60-90 minutes): One year after the last Experimental Session (10 months after the 'Measuring PTSD After Sessions' visit), you will be asked to come in for one more interview session to see if your PTSD symptoms continue to improve, stay the same, or worsen over time after the study.

All procedures for this study will be performed at the VA Loma Linda Healthcare System.

3. WHAT IS EXPECTED OF YOU IN THIS STUDY?

Your participation and feedback during this study is important to researchers. To help us make sure we provide them with the best information possible, we want you to know what is expected of you before you decide to take part. You will be expected to:

- Be flexible about taking the appointments that are offered most of the time because there is a limited time frame for each type of visit
- Take the study drug as instructed
- Tell the study staff about any side-effects you have during the study
- Keep your study appointments - if you miss an appointment, please contact the study team to reschedule as soon as you know you will miss the appointment
- For female participants - tell the investigator or research staff if you believe you might be pregnant
- Provide a urine sample prior to each MDMA session and provide a blood sample at the time of enrollment
- Fill out your diaries as instructed
- Complete your questionnaires as instructed
- Refrain from taking any herbal supplements, non-prescription and prescription medications unless discussed with the study doctor one week prior to MDMA session.
- Ask questions as you think of them
- Not take part in any other research study that is testing another medicine or treatment (This is to protect you from possible injuries and make sure the researchers get valid results about the safety and effectiveness of the study drug)

4. WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE, IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur. The study team will watch you closely for possible health problems or side effects that happen while you are taking part in the study. If side effects happen, you will be treated if needed.

Tell the study team about any side effects or health problems you have while taking part, even if you do not think that the side effects were caused by the study drug.

Possible risks, discomforts or inconveniences expected for this study include:

- The **interviews and questionnaires** during the study involve no specific risks or discomforts beyond what is expected during a standard clinical interview. You may feel upset thinking or talking about your experiences and emotions, or you may feel boredom or fatigue. Answering questions about thoughts you may have of hurting or killing yourself may be upsetting. The risk associated with recording these interviews is the risk of loss of confidentiality; the risk of this happening is very low.
- **Blood sampling** – during the study, a small amount of blood will be taken. This allows the study team to know it is safe for you to take part in the study.
    - You may feel a little discomfort, bruising, bleeding or swelling where the needle goes in.
    - There is also a very small risk of infection where the needle goes in**.**

Side effects of the study drug. As of October 2016, more than 1,260 people have been given MDMA in clinical research settings without any serious unexpected problems happening. No long-term serious side effects have occurred as a result of taking the study drug in a research setting.

Side effects that will likely happen within minutes to hours of taking the study drug and go away by the next day:

- **Blood pressure and heart rate:** the effects of MDMA usually last six to eight hours with the first and second dose. At the dose used in the study, the increases in blood pressure and heart rate are likely to be moderate. Heart rate may increase by approximately 30 beats per minute, on average. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in people with pre-existing heart of blood vessel conditions. These serious problems could include an irregular heartbeat, heart attack or stroke. We will look for existing heart problems before you are allowed to be in this study. While this does not guarantee that no heart problems will occur, it does reduce the risk of this happening.

- **Temperature Increase:** MDMA has been found to increase body temperature but this effect is temporary and not harmful in a controlled setting. Fever or body temperature >41ºC/105.8ºF has been found in people ingesting “Ecstasy” in uncontrolled environments and often dancing or engaging in intense exercise. In MDMA studies, participants mostly remain seated or laying down. Your temperature will also be closely monitored along with heart rate and blood pressure. Studies so far have shown a small increase in body temperature which does not reach a dangerous level.

The following side effects may occur after taking the study drug, are typically not severe, and resolved within 1-4 days:

- Teeth grinding or tight jaw muscles (64%)
- Lack of appetite (50%)
- Dizziness (45%)
- Changes in temperature (feeling too hot or too cold) (40%)
- Muscle tension (35%)
- Changes in vision, hearing or bodily sensations (numbness, tingling) (12-33%)
- Insomnia and drowsiness (1.4-62%)
    - ***You should not drive or use machinery immediately after Experimental Sessions (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 noticed up to two or three days later, while some participants feel their mood is better, 20% to 30% feel that it is worse. This can include thoughts of suicide. Overall incidence of serious suicidal ideation or behavior in studies conducted in controlled lab conditions was low.
    - After receiving MDMA in MAPS sponsored studies, three participants reported suicidal ideation and/or behavior however these events were thought to be unrelated to MDMA; for example these instances of suicidality occurred either prior to receiving the study drug or after receiving placebo.
- Anxious or jittery feeling: In past studies, some participants with an anxiety disorder who received MDMA (70.1%) 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 no able to deal with these experiences in a way that helps you, the study team will work with you to deal with these feelings.

- **Addiction/Abuse:** Some animal studies suggest that MDMA may have potential for abuse or addiction, though to a much lesser degree than amphetamine. Animal studies appear to show lower rates of symptoms of physical dependence when compared to other drugs. In one study, monkeys displayed less effort to obtain MDMA compared to other stimulants.

The following are possible side effects that are not likely to occur (rare):

- **Brain/cognitive effects:** Only one study has looked at brain scans of people before and after they got one or two moderate doses of MDMA. This study did not show any changes in the brain following MDMA, though it is possible that the changes were too small to notice. Most research has been conducted on "Ecstasy" recreational users, which means the researchers did not know what chemical or amount was actually taken.

  Studies of people receiving only a few doses of MDMA in a laboratory setting have not found any lasting problems with memory or attention. 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. Some animal studies suggest that brain damage is possible at high doses of MDMA. In other animal studies, neurotoxic or harmful effects to brain cells was not found.

- **Immune System:** You may have a less active immune system for two or three days after taking MDMA. This may make you more likely to become sick with a cold or other infection during this time. The frequency of this potential side effect is unknown and it is also unknown how vulnerable you will be to an exposure of SARS-CoV2 (the virus that causes COVID-19 disease). Please see COVID-19 section on page 16 for precautions we are taking.

There have been some serious problems, even deaths, associated with the use of "Ecstasy" (illegal substance alleged to contain MDMA) *outside of controlled clinical or research settings.* Because "Ecstasy" is sold illegally, there is no way to know what substance(s) or combinations of substances was taken. Also, we do not know the amount or how frequently a substance(s) was taken. "Ecstasy" has caused problems such as:

- high fever
- brain swelling associated with drinking too much water
- convulsions
- severe anxiety, depression or paranoid thinking

Since you will be receiving moderate amounts of research-grade MDMA, 3 times, in a controlled setting with a trained study team who will be closely monitoring your physical and psychological reactions, these problems **are not expected to occur** either during or after the Experimental Sessions. 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.

Other Drawbacks

Being in this study requires a long-time commitment. You will not be compensated monetarily for taking part, including missed time off of work. If you are not able to meet the time commitment for any reason, you should not be in the study.

If you are tested for drugs of abuse within three days of each Experimental Session, you may test positive. The study team 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 team to verify that you are in this study. This card may not protect you from discipline at work or loss of employment. Think carefully about enrolling in this study if you are a federal employee in a testable position. The study doctors will discuss when and how to present the information card. The card will not prevent you from being stopped or cited if you are driving erratically or poorly so you should not operate machinery or drive a car until you feel normal again.

It is possible that after you stop taking psychiatric medications (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 team. If you have to start taking medicine again, then the study doctors will have to take you out of the study.

COVID-19: Taking part in this study will require a number of in-person visits that will be several hours long, including the 8-hour Study Drug Sessions. This may increase your risk of becoming infected with SARS-CoV-2. Due to the COVID-19 pandemic or other unforeseen circumstances, there may be alterations in how some of your visits are conducted; for example, by telephone or through video visits instead of in person for any visit that does not involve giving you study drug. When possible, this will be done to reduce your possible exposure.

- **COVID-19 Precautions**: This study will be taking place during the worldwide COVID-19 pandemic. We are committed to your safety and are taking the following steps to minimize the risk of COVID-19 transmission:
  - COVID-19 testing will be completed prior to experimental sessions, in accordance with local hospital policy
  - COVID-19 Screening will be completed:
    - by the study team over the phone within 24 hours of a face-to-face visit
    - by hospital staff upon entering the facility on the day of the face-to-face visit, including taking your temperature.

- Proper social distancing of at least six feet between individuals during face-to-face visits
- Masks will be worn by all individuals (cloth mask, surgical mask or N95; bandanas, gaiters or vented masks are not acceptable). If you do not have a mask on the day of your appointment, one will be provided at no cost to you.
- Handwashing station and/or hand sanitizer will be available during all face-to-face visits
- Proper disinfection of patient care areas will be completed before and after each participant visit
- The Study Team will ask you about your habits prior to in person visits, and together you will figure out a safe plan for reducing risk while attending in-person visits. This plan may include testing for the virus, receiving the COVID-19 vaccine, isolating at home, or other changes to your habits.
    - Any COVID-19 testing requested by the study team will be offered at no cost to you through VA Loma Linda Healthcare System.

Reproductive Risks: Effects of MDMA on the growth and development of an unborn baby are not known; therefore, you will not be allowed to take part in the study if you are pregnant. If you get pregnant after you have had at least one Experimental Session, the study doctors and the VA will ask you about your pregnancy and keep track of your pregnancy to know about the outcome.

Those who are able to get pregnant and are sexually active must use one of the allowed birth control methods: intrauterine device (IUD), injected or implanted hormonal methods, abstinence, birth control pill plus a barrier contraception or double barrier contraception. Two forms of contraception are required with any barrier method or birth control pill (i.e. condom + diaphragm, condom or diaphragm + spermicide, birth control pill + spermicide or condom). Not being of childbearing potential is defined as permanent sterilization (tubal ligation or hysterectomy), postmenopausal, or assigned male at birth. The study team will explain these methods to you and will help you decide which might be best for you, and they can suggest where you can get more information and advice.

If you are 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 you may be pregnant or are worried that you may become pregnant, you must tell your study team immediately. If you should become pregnant during the study, study doctors will help you get proper advice and direct you to proper care for you and your unborn baby. If you become pregnant, you will discontinue treatment but remain in the study for follow-up purposes.

Confidentiality risks: We are collecting sensitive information about you which could become known to someone who is not involved with the study. Although we will take precautions to protect your privacy, there is always a risk of loss of confidentiality. Because this is a research study, you will be assigned a study number and only the study staff will have access to the records that link you to your study number. These records will be kept in a secure, locked cabinet at the study site. All records, including those which could provide identification, will be kept in a locked office.

To further help us protect your privacy, the investigators have applied for a Confidentiality Certificate from the Department of Health and Human Services. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

5. WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

Your symptoms of PTSD may improve while taking part in this study and you may continue to improve over time even after completion of this study. However, this cannot be guaranteed and there may not be any direct benefit for you by taking part in this study. Information from this

study may help doctors and researchers to improve treatment for PTSD and relationships in the future.

6. WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You do not have to take part in this study to get treatment for your PTSD symptoms. You are free to say no. Alternatives include not to participate. There are approved medications that may help treat your symptoms of PTSD and other forms of psychotherapy that you could try. If you are currently having psychotherapy and/or taking medications, you could continue with those for a longer period of time. The study team can discuss the options and their potential risks and benefits with you.

7. HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

During the study, the study team will collect information about your health and certain types of personal information. This may include your name, birth date, contact information, social security number, gender and ethnic origin. All blood samples and paper documents sent to MAPS for safety reporting will be identified by a code number only and no information that can directly identify you will be sent to anyone outside of the VA Loma Linda Healthcare System. By signing this consent form, you agree that we may collect, use and release your personal health information for the purpose of this research study.

Although the information obtained about you during the research study will be kept strictly confidential, the information will be available to persons connected to this study including the Department of Veterans Affairs, MAPS, Research Advisory Panel of California (RAPC), Loma Linda Veterans Association for Research and Education (LLVARE) and may be released to agencies as required by law, such as the Food and Drug Administration (FDA).

Detailed information about others that have access to your health information as part of the study is included in Section 9 on page 20 this document. Offices within the VA/VHA that are responsible for oversight of VA research may also have access to your information in the performance of their duties. Information collected about you will be kept in a locked office to protect your privacy.

The results of this study may be published, but your identity will not be revealed in any publication without permission. Some results from the study will be made publicly available sometime after the study finishes. This may include a summary of the results, which will be available on the internet. 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.

We will not include information about your study participation in your medical record. However, any study procedure that may affect your regular care (such as lab tests results, medication changes, blood pressure readings, physical examination findings), will be entered into your medical records to make sure your care providers are fully informed about your well-being.

Private information and specimen collected as part of this research will not be used or distributed for future studies.

9. HEALTH INFORMATION PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records such as existing medical history and mental health records, lab results, HIV and HCV status, drug or alcohol use and treatment and new health information collected during the study.

The research team may also need to disclose your health information and the information it collects to others as part of the study progress. Others may include MAPS, for safety event reporting, the Institutional Review Board, Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), VA Research Compliance Office, and the Government Accountability (GAO).

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, Dr. Shannon Remick and Allie Kaigle, PharmD, BCPP and their research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time. Records collected during this trial will be kept by the study team for six years after the study closes.

10. WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. The sponsor of this study, VA, will cover the costs that are directly related to the research. This includes the costs for all tests and psychotherapy sessions that are part of the study; this includes the psychological and laboratory testing, medical examinations, EKG and study drug). If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

For research-related injuries, you can receive medical care from the VA, free of charge. Further medical care will be based on your VA eligibility, for instance some veterans are required to pay co-payments for medical care and services provided by VA and pay for medical care received outside of a VA Medical Center. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

The VA is not obligated to reimburse medical expenses due to non-compliance with study procedures contained in this informed consent, such as taking medications you have been instructed not to take or intentionally misinforming the study team on medications you have taken, or otherwise communicated to you by study personnel. You do not, however, waive any legal rights by signing this consent form.

Payment During Participation:

You will also be compensated $50 for travel expenses on each scheduled in-person research visit after consent. There will be no pay for unscheduled contacts or phone calls. Your study team will arrange these payments to you.

Payment for taking part in a research study may be considered taxable income. If payments total more than $600.00 in any one calendar year, the study team will have to report this to the IRS using a 1099 (Miscellaneous Income) form. The 1099 form will be issued to you and a copy will be sent to the IRS. You will need to provide your social security number to your study team, if this applies to you. Your social security number will not be included in any study records. The Non-Profit Corporation that is assisting your site with payment processing is the Loma Linda Veterans Association for Research and Education (LLVARE).

11. DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this research study is voluntary. If you decide to take part, you can stop at any time. If this happens, you may be asked to return for one final visit for safety reasons. You will get the same medical care from VA Loma Linda Healthcare System whether or not you take part in this study. Refusal to take part in the study will involve no penalty or loss of benefits to which you are otherwise entitled.

If you agree to take part, and then later change your mind, the decision to discontinue taking part in the study will have no impact on your employment, ratings, subsequent recommendations, or academic progress. You may change your mind about taking part in this study at any time without any penalty or loss of benefits. You will still receive the same standard of care that you would otherwise receive.

If you decide to withdraw, you must notify the study team. The study team may continue to use the information and blood samples that have already been collected in ways described in this consent form, but no new information will be collected after you withdraw.

It has been explained to you that you do not have to take part in this study and you are free to withdraw at any time. Your decision not to participate or to withdraw will involve neither penalty nor loss of VA or other benefits to which you might be otherwise entitled. Should you choose to withdraw:

1) You can discontinue the study drug and continue study visits. Please talk to the study doctor before stopping the study drug so that it can be stopped safely.
2) You can discontinue the study drug and discontinue study visits. You will be asked to come for a final visit. This will be to check your health and any effects of the study drug on your body up until that point. Your study team will continue use your records to gather data for the study. The study team may also find out more information about your health using publicly available sources at the end of the study. This is important for the overall results of the study. However, you will not be contacted.
3) You can discontinue your participation in the study completely and your study team will only use the data that has already been collected. You will be asked to come for a final visit to check your health and safety, and you will be asked to sign a form that stops the study team from collecting any new information after you withdraw.

12. RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

The study doctor may stop you from taking part in the study at any time, even if you want to continue. Some reasons may include:

- For your safety – for example, if your body has a bad reaction to the study drug

- If the study drug is not the best choice for you, or if you need a treatment that is not allowed while in this study (such as restarting a medication for depression or anxiety)
- If your illness becomes worse
- If you do not keep appointments or follow study procedures
- If you are a woman and you become pregnant or would like to become pregnant
- If the study is canceled by the FDA or IRB. The VA, the FDA, or the IRB may decide to stop the study at any time.

Your participation may also be terminated without your consent if the study doctor feels it is in your best interest. The consequences of the decision to withdraw from the research, if any, and procedures for an orderly termination of participation will be discussed with you by the study physician.

13. WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Sometimes new information about the study drug is received. You will be told if any relevant new information becomes available that may affect your willingness to continue taking part in the study. If this happens, your study team will contact you as soon as possible, and will discuss whether you should continue in the study. If you decide to continue in the study, you may be asked to sign a new consent form. If you choose to stop, the study doctor will discuss your options for future care and treatment.

Also, if new information becomes available, your study doctor may stop your participation without your consent. If this happens, the reasons will be explained, and arrangements made for your care to continue.

14. WHO COULD PROFIT FROM THE STUDY RESULTS?

MAPS is paying for the study drug and the VA Loma Linda Healthcare System is paying for the study to take place at this facility. Your blood samples and medical or mental health information will not be used for commercial profit. However, the results of this study may be used to promote approval of the drug by the FDA. You will not be compensated if the drug is approved and marketed.

15. WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS OR CONCERNS RELATED TO THE STUDY?

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the

Office of Research Administration at (909)825-7084 ext. 6050 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

If you have any questions about the availability of medical care or if you believe you have experienced a research-related injury as a direct result of participation in the study, you should immediately contact:

- Dr. Shannon Remick or Allie Kaigle, PharmD, BCPP at (909) 583-6361 during the day on weekdays

For after hours or weekends call:

- Dr. Shannon Remick at 909-330-6464
- Allie Kaigle, Pharm D, BCPP at 909-787-4814

If you have questions, concerns, or complaints about the study, you may call the study doctor or study staff at ext. 6361.

If you wish to contact an impartial third party not associated with this study or have questions or concerns about the research or your rights as a research subject, you may contact the Administrative Officer, Office of Research Administration, VA Loma Linda Healthcare System, 11201 Benton Street (151), Loma Linda CA 92357, telephone (909) 825-7084 x6050.

16. AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY:

The study has been explained to me and all of my questions answered. I have been told of the risks or discomforts, possible benefits of the study, and other choices of treatment available.

I have read the consent form, or it has been read to me. My rights as a research subject have been explained to me and I voluntarily consent to participate in this study. The study has been described to me and that description has included explanations of what the study is about and how and why it is being done. I will receive a signed copy of this consent form and a copy of the California Bill of Rights for Human Subjects in Medical Research.

Signing this document below is an indication of my acceptance and understanding of what is expected of me and of the study team during participation.

Please do not sign until all of your current questions have been answered.

Participant Name: _____ Date:_____

Title of Study: _MDMA-Assisted Psychotherapy for Combat Veterans with Treatment-Refractory PTSD._

Principal Investigator: _Shannon Remick, MD___ Co-Principal Investigator: _Allie Kaigle, PharmD, BCPP

VA Facility: __VA Loma Linda Healthcare System__.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date