Form Approved Through 09/30/2007 OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.

Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*
Treatment manual development for MDMA-assisted therapy

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)
Number: PAR-03-108 Title: NIH SMALL RESEARCH GRANT PROGRAM (R03)

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR — **New Investigator** ☐ **No** ☒ **Yes**

3a. NAME (Last, first, middle)
Mithoefer, Michael C

3b. DEGREE(S)
MD

3h. eRA Commons User Name

3c. POSITION TITLE
Psychiatrist, investigator

3d. MAILING ADDRESS *(Street, city, state, zip code)*

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Contractor

3f. MAJOR SUBDIVISION
Multidisciplinary Association for Psychedelic Studies

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: XXX-XXX-XXXX FAX: XXX-XXX-XXXX

E-MAIL ADDRESS:
Mmit@bellsouth.net

4. HUMAN SUBJECTS RESEARCH ☐ No ☒ Yes

4b. Human Subjects Assurance No.
None

4c. Clinical Trial ☒ No ☐ Yes

4d. NIH-defined Phase III Clinical Trial ☐ No ☐ Yes

4a. Research Exempt ☒ No ☐ Yes

If "Yes," Exemption No.

5. VERTEBRATE ANIMALS ☒ No ☐ Yes

5a. If "Yes," IACUC approval Date

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
1/01/06	1/01/08	$50,000	$62,500	$100,000	$125,000

9. APPLICANT ORGANIZATION
Name: Multidisciplinary Assoc for Psychedelic Studies
Address: 3 Francis St.
Belmont MA 02478

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
592751953
DUNS NO. Cong. District

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Richard E Doblin PhD
Title: President, MAPS
Address: 3 Francis St.,
Belmont MA 02478
Tel: 617-484-8711 FAX:
E-Mail: Rick@maps.org

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Richard E Doblin PhD
Title: President, MAPS
Address: 3 Francis St.
Belmont MA 02478
Tel: 617-484-8711 FAX:
E-Mail: Rick@maps.org

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)* DATE

15. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)* DATE

DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to **public** health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The aims of this project are to develop and standardize 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy as a novel treatment for posttraumatic stress disorder (PTSD). PTSD affects up to 20% of crime victims and veterans, reducing quality of life and productivity. The investigators plan to develop a treatment manual describing standardized therapy procedures in order to train therapists to perform MDMA-assisted therapy in larger Phase II and Phase III studies. When completed, the manual will include evaluative guidelines and associated measures of therapist adherence and competence. The investigators will develop the manual through the use of previous anecdotal accounts of MDMA-assisted therapy, and by observing and reviewing audio and video recordings of psychotherapy sessions. When appropriate, the manual will also be informed by findings from Phase I studies of MDMA in humans. Session recordings are from a randomized, placebo-controlled, double-blind study of MDMA-assisted psychotherapy in people with PTSD and an open-label study continuation for any participants who received placebo during the double-blind study. The principal investigator and two co-investigators will observe, review and examine session recordings and develop a manual for each stage of MDMA-assisted psychotherapy. All investigators will assist in reviewing and editing successive manual, guideline and measure drafts. During maual development or immediately afterwards, the investigators will create evaluative guidelines for each stage of MDMA-assisted therapy. Once they have produced a treatment manual, the investigators will create brief measures of therapist adherence and competence for assessing therapists trained in MDMA-assisted therapy with the manual, with measures at an appropriate level of detail for a novel intervention. The production of the treatment manual and attendant measures will permit further research into an innovative and potentially promising means of treating PTSD. If data from pilot studies and other Phase II studies provide evidence of safety and efficacy, standardized procedures for conducting the therapy will lead to rapid development of this intervention.

PERFORMANCE SITE(S) (organization, city, state)

Offices of Michael C Mithoefer, MD
Audiotaping and videotaping of participants taking place in the ongoing pilot study of MDMA-assisted psychotherapy in people with PTSD
Offices of June May Ruse PsyD, offices of Michael C. Mithoefer MD
Reviewing literature on MDMA-assisted therapy, audiorecordings and videorecordings of sessions, editing treatment manual draft, creating evaluative guidelines and measures of therapist adherence and competence
Offices of Michael C. Mithoefer MD or June May Ruse PsyD
Conferring between investigators, sponsor and research consultants on matters of treatment manual develoment, occurring at least once during the proposed period of grant award
Offices of Rick Doblin PhD, Lisa Jerome PhD, Elizabeth Gibson, Sherry Falsetti,, Michael C and Ann T Mithoefer, and June May Ruse PsyD.
Editing treatment manual, guidelines and measures of therapist adherence and competence

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Michael C. Mithoefer MD		MAPS	, Principal Investigator
Rick Doblin PhD		MAPS	Co-investigator
Elizabeth Gibson MS		MAPS	Co-investigator
Lisa Jerome PhD		MAPS	Co-investigator
Ann T. Mithoefer BSN		MAPS	Co-investigator
June May Ruse PsyD		MAPS	Co-investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
Sherry Falsetti PhD		Research Consultan

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/registry/index.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Disclosure Permission Statement. Applicable to SBIR/STTR Only. See SBIR/STTR instructions. ☐ Yes ☒ No

The name of the principal investigator/program director must be provided at the top of each printed page and each continuation page.

RESEARCH GRANT

TABLE OF CONTENTS

Appendix *(Five collated sets. No page numbering necessary for Appendix.)*

Check if Appendix is Included

Appendices NOT PERMITTED for Phase I SBIR/STTR unless specifically solicited. ☒

Number of publications and manuscripts accepted for publication *(not to exceed 10)* 10

Other items (list):

Ruse J, Jerome L, Mithoefer M, Dobin R, Gibson E (2005) MDMA-assisted psychotherapy for the treatment of Posttraumatic Stress Disorder; A revised teaching manual draft. Published on-line: http://www.maps.org/mdma/ptsd_study/treatment-manual.html

BUDGET JUSTIFICATION PAGE MODULAR RESEARCH GRANT APPLICATION						
	Initial Period	**2nd**	**3rd**	**4th**	**5 th**	**Sum Total (For Entire Project Period)**
DC less Consortium F&A	25,000 *(Item 7a, Face Page)*	25,000	25,000	25,000		100,000 *(Item 8a, Face Page)*
Consortium F&A						
Total Direct Costs	25,000	25,000	25,000	25,000		$ 100,000

Personnel

Michael C Mithoefer MD (Principal Investigator, 50%) He is performing all psychotherapy sessions for the ongoing study. He will coordinate and edit audio and video recordings of study participants for treatment manual development. He will examine session recordings or transcripts, collaborate on all aspects of manual development, including writing and reviewing text and evaluative guidelines, and designing measures of therapist adherence and competence.

June May Ruse PsyD (Co-investigator, 40%) will continue to observe, examine, analyze and synthesize audio recordings of experimental therapy sessions from the ongoing study, and she will undertake the same process with video recordings. She will construct and edit the main body of the treatment manual, along with Michael Mithoefer, and she will design evaluative guidelines and measures of therapist adherence and competence.

Ann T. Mithoefer BSN (Co-investigator, 20%) is performing all psychotherapy sessions for the ongoing study. She will coordinate and edit audio and video recordings of study participants for treatment manual development. She will collabiorate on all aspects of treatment manual development, including writing and reviewing text, guidelines and measures.

Lisa Jerome PhD (Co-investigator, 0%-supported by sponsor) provides the co-investigators with input about MDMA research and assists in editing the treatment manual draft. She will continue to edit the body of the treatment manual draft, evaluative guidelines, and measures of therapist adherence and competence with attention to readability and areas informed by MDMA research.

Rick Doblin PhD (Co-Investigator, 0%-supported by sponsor) is the study sponsor and also will continue to assist in editing the treatment manual, evaluative guidelines and measures of therapist adherence and competence.

Elizabeth Gibson PhD (Co-investigator, 0%-supported by sponsor) will provide assistance in editing the treatment manual and evaluative guidelines, and measures of therapist adherence and competence, using her experience in psychotherapy research, and offering advice on manual structure and content.

Consortium

N/A

Fee (SBIR/STTR Only)

N/A

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

None.

Clinical:

Offices of Michael Mithoefer MD, SC. Audio and videorecordings of psychotherapy sessions are made at this location. The principal investigator is already engaged in a study and has installed audio recording and playback equipment, including capacity to record to compact disc. There is space available for videorecording equipment. Offices have locked file drawers for data storage. (con't)

Animal:

None

Computer:

Computers will be used to edit recordings of psychotherapy sessions, and to write the treatment manual. These include computers at the offices of Michael Mithoefer (address above), Ann Mithoefer BSN (address above), June May Ruse PsyD, (con't)

Office:

Offices where therapy session recordings will occur will be the offices of Michael Mithoefer MD, address listed above. (con't).

Other:

None

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Location and appropriate supports for psychotherapy sessions at the offices of Michael Mithoefer, including furniture, audio playback equipment (for music presentation during psychotherapy session), blood pressure, pulse and body temperature monitoring equipment, crash cart, refrigerator for storing beverages (water or electrolyte-containing beverages), safe for storing drug (compliant with DEA regulations), space for overnight stay. Dr. Mithoefer owns the office and thus has full control over scheduling psychotherapy sessions and equipment maintained in the office.

Audio recording equipment, at the offices of Michael Mithoefer records sessions to compact disc. There is capability of editing session recordings and producing copies for the participant and for June May Ruse.

Audio playback equipment, in the offices of Michael Mithoefer and June May Ruse; includes compact disc players that can play psychotherapy session recordings.

Computers for document creation, review and editing, and for electronic communication between investigators are located at the offices of Michael and Ann Mithoefer, June May Ruse, Lisa Jerome, Rick Doblin, Elizabeth Gibson and consultant Sherry Falsetti. All machines are capable of standard word processing and are connected to the internet. (con't)

Resources Page (con't)

Clinical Offices of Michael Mithoefer MD, SC, As owner of the site, Mithoefer is expected to be able to schedule all psychotherapy sessions and record sessions of consenting participants.

Computer: Office of Lisa Jerome PhD, Rick Doblin, Elizabeth Gibson, and consultant Sherry Falsetti. All computers contain word processors and are connected to the internet, and all computers can handle standard document editing. In addition, computers at the offices of Michael Mithoefer possess software for editing audio recordings. Except for Ann Mithoefer, co-investigators and the consultant do not share the same office and live in different states

Office: Observation, review and analysis of recordings will be performed in the offices of Michael Mithoefer and the offices of June May Ruse, PhD, as listed above. Additionally, review and editing of text will be done in the offices of Lisa Jerome, Rick Doblin and Elizabeth Gibson, listed on previous page and above. All offices contain working computers suitable for word processing, and the office of Michael Mithoefer contains audio recording equipment and equipment suitable for performing MDMA-assisted psychotherapy. The offices of June May Ruse and Lisa Jerome possess locked file cabinets. The office of June May Ruse has audio playback equipment.

Major Equipment

Locked file drawers for storing data and recordings will be at the offices of Michael Mithoefer, June May Ruse and Lisa Jerome. File cabinets and drawers will be used to store recordings in the case of Mithoefer and Ruse, and can be used to store documents in the case of Jerome.

Research Plan

A. Specific Aims

Posttraumatic stress disorder (PTSD) is a serious and debilitating mental illness resulting from experiencing one or more traumatic events, such as physical or sexual assault or participating in active combat. There is a need for an array of possible treatments for this condition. Treatment of this psychiatric disorder is currently limited to a few pharmacological and psychotherapeutic treatments (Bradley et al. 2005), and a significant number of people do not find these treatments sufficiently helpful (Hamner et al. 2004). Drawing on evidence from anecdotal reports and controlled and uncontrolled research studies, the investigators hypothesize that 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy may alleviate symptoms and improve quality of life for people with PTSD, including people who have not responded well to accepted pharmacological or psychotherapeutic treatments for this condition. If findings from a pilot study of MDMA-assisted psychotherapy in 20 people with treatment-resistant PTSD under way in South Carolina are promising, then additional Phase II and Phase III studies are planned to test the efficacy of MDMA-assisted therapy as a treatment for PTSD. A manual of standardized procedures for MDMA-assisted psychotherapy must be developed before these larger Phase II and Phase III studies can be conducted. The proposed project will be for the development of the first treatment manual for MDMA-assisted therapy in people with PTSD, including evaluative guidelines and measures of therapist adherence and competence. Treatment manual development and conducting larger studies are intended to lead to the development of an innovative option for treatment of PTSD that will improve quality of life in people suffering this debilitating mental illness.

The proposed project is intended to meet specific aims and goals. The aims and goals are the following:

1. To develop a treatment manual containing standardized methods, procedures and evaluative guidelines for conducting MDMA-assisted therapy for use in conducting multi-site studies of MDMA-assisted therapy in people with posttraumatic stress disorder.
2. To develop measures of therapist adherence and competence in performing MDMA-assisted psychotherapy as represented in the treatment manual, and to begin developing a training program for therapists who will perform MDMA-assisted psychotherapy in research studies.

In the near future, investigations of MDMA-assisted psychotherapy are planned to take place in Israel, Switzerland and Spain, and further Phase III studies will be needed to test the efficacy of MDMA-assisted psychotherapy. The investigators will use a treatment manual and a training program to teach therapist-investigators to perform this therapy in a standardized manner. Developing a treatment manual that describes and encapsulates these methods and procedures will be an essential part of performing further research into the safety and efficacy of MDMA-assisted psychotherapy in people with PTSD.

This novel combination of psychotherapy and pharmacological adjunct may be especially helpful in treating people with PTSD symptoms that do not resolve after receiving currently recognized treatments for PTSD. As such, this therapy could benefit people who continue to suffer from PTSD despite receiving psychotherapy or medication. The intervention itself is unusual in its use of psychotherapy along with a drug adjunct, and its potential success may lead to further research into the potential of the use of psychotherapy adjuncts.

B. Background and Significance

Theoretical Background: Posttraumatic stress disorder (PTSD) occurs in response to a traumatic event or events. It is most likely to occur following an event that involves perceived personal threat, such as rape or physical assault (Breslau 1998). Approximately 10% to 30% of people who experience a major trauma go on to develop PTSD, giving it an estimated 8% prevalence in the general population (Kang and Hyam 2005; Kessler et al. 1995; Resnick et al. 1993). Criteria for PTSD include exposure to a significant traumatic event accompanied by an intense acute emotional response, persistent re-experiencing of the event or aspects of the experience, persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life, and persistent symptoms of increased arousal, with one month of persistence for acute PTSD and three or more months for chronic PTSD (DSM-IV). In the National Comorbidity Study, the median time to remission was 36 months with treatment and 64 months without treatment, but symptoms were documented as lasting up to 10 years (Kessler et al. 1995). In our ongoing study described above, treatment resistant subjects' symptoms have persisted for up to 43 years.

People with this disorder may experience impaired work productivity, difficulties with relationship maintenance and decline in overall health (Brady et al. 2000). Studies in humans and non-human animals suggest that ongoing symptoms and stress arising from untreated PTSD may be neurotoxic in hippocampal areas (Bremner 1999; Ling 1981; Rauch 1996; Sapolsky 1990; Shin 1997; Wolkowitz, 1990). Currently, there are two approved pharmacological treatments for PTSD, paroxetine (Paxil) and sertraline (Zoloft), and a small number of recognized psychotherapeutic treatments (Brady et al. 2000; Marshall et al. 2001; Montgomery and Bech 2000). Psychotherapeutic interventions for PTSD include cognitive-behavioral, exposure therapy, stress inoculation training, (including anxiety management), and insight-oriented psychotherapy (Foa et al. 1999; Jaycox et al. 2002; Krupnik 2002; Resick and Schnicke 1992; Resick et al. 2002). In November 2004, the American Psychiatric Association (APA) published Practice Guidelines for the treatment of PTSD. The three psychotherapeutic interventions recommended for established PTSD are cognitive and behavior therapies, eye movement desensitization and reprocessing (EMDR) and psychodynamic psychotherapy.

These procedures tend to share several elements in common, including exposure to trauma-related material, learning behavioral or cognitive strategies, anxiety management, and focusing on positive experiences occurring in the present. Although the APA endorses the above therapies in their Practice Guidelines, it is noteworthy that they also imply the need for research into more effective treatment techniques stating "there is a paucity of high-quality evidence-based studies of interventions for patients with treatment-resistant PTSD…." (Ursano et al. 2004).

PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. A significant minority of people still experience some PTSD symptoms or retain the diagnosis even after receiving a recognized pharmacotherapy or psychotherapy treatment (Hamner et al. 2005; Resick et al. 2002), Resick et al (2002) reported that at posttreatment, 53% of women receiving Cognitive Processing Therapy, and 53% of the women in the Prolonged Exposure condition were PTSD negative on the CAPS in their intent to treat sample, with 47% still PTSD positive at the end of a course of treatment. Foa et al. (1999) report similar results with success ranging from 40% to 60%.

People with PTSD may have to undergo more than one treatment, or combine treatments, before symptoms are reduced (Hamner et al. 2005). Developing treatments that work for a greater number of people will help

reduce the suffering and public health costs of PTSD. Anecdotal reports (Adamson 1985; d'Otalora 2000) and preliminary findings from a current study suggest that MDMA-assisted psychotherapy may serve as an innovative treatment for PTSD, and that it might be helpful for people who have not responded well to the available therapies. MDMA-assisted psychotherapy may also be more strongly focused on dealing with and resolving issues of interpersonal trust and emotional numbing than psychotherapies that focus chiefly on resolving anxiety or avoidance both as a result of the subjective effects of MDMA and the therapeutic procedures used during MDMA-assisted psychotherapy. MDMA reportedly enhances access to emotionally charged material, feelings of closeness toward others and acceptance of the self and others (Greer and Tolbert 1986; Metzner and Adamson 2001), and the therapists support and encourage engagement in emotionally intense thoughts, feelings and memories throughout the course of therapy, and especially during MDMA-assisted sessions.

Background and Review of Treatment Components: MDMA is a ring-substituted phenylisopropylamine derivative with a unique profile of psychopharmacological effects that make it well suited to intensive psychotherapy. Many researchers hypothesize that MDMA belongs to a new class of psychoactive agents, called entactogens (Nichols 1986), producing feelings of closeness to others, empathy, well being, and insightfulness, with little perceived loss of control (Nichols 1986; Shulgin and Nichols 1978). There is considerable previous human experience with MDMA in a psychotherapeutic context. Therapists have performed MDMA-assisted psychotherapy in the US and Europe (Gasser 1994; Greer and Tolbert 1986; Greer and Tolbert 1998; Widmer 1998). Prior to criminalization, some therapists employed MDMA in psychotherapy to treat a number of psychological problems and psychiatric disorders (Greer and Tolbert 1986; Widmer 1998). Though no well-controlled clinical trials were performed at the time, these therapists concluded that MDMA could be safely administered and was clinically useful in treating various sub-clinical or clinical psychiatric conditions, including PTSD (Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998).

MDMA shares some psychological effects with stimulants and hallucinogens, but also seems to possess a unique pharmacological profile (Cami et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2003). MDMA reportedly increases rapport between patient and therapist and increases a sense of acceptance for the self and other (Greer and Tolbert 1998), though studies in healthy humans currently offer only tentative support for these effects (Harris et al. 2002; Tancer and Johanson 2003). An imaging study detected reduced activity in the left amygdala after 1.5 mg/kg MDMA (Gamma et al. 2000), suggesting that MDMA may reduce or alter either perception or attention to fear-inducing stimuli or the experience of fear (Adolphs 1999; LeDoux 1998), a potentially significant effect, because increased amygdalar activity differentiates people who developed PTSD after a traumatic event from people who did not develop PTSD (Shin et al. 2005). The subjective effects of MDMA specifically relevant to PTSD include increased recall, including recall of emotional material, specific increases and decreases in anxiety, altered perception of the meaning of objects or thoughts, and increased friendliness and closeness to others (Cami et al. 2000; Farre et al. 2004; Greer and Tolbert 1986; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003; Vollenweider 1998). MDMA is associated with increased accessibility of intensely emotional thoughts, feelings and memories without a subsequent decline in recall for the experience or the emotionally intense material afterwards (Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004). These effects may be the direct result of pharmacological actions, as on serotonin release (Liechti et al. 2000; Liechti and Vollenweider 2000a) or they may arise indirectly through altering cognition, emotion, and social interaction. For instance, dopamine may increase arousal and positive mood (Liechti and Vollenweider 2000b), while activity at 5HT1A receptors, reduced learned associations that lead to adverse outcomes in rodents (Guimaraes et al. 1993).

Specific psychotherapeutic methods and procedures enhance and optimize the potentially therapeutic effects of MDMA. Helping people articulate goals for the MDMA-assisted session and discussing them with the patient beforehand, encouraging confrontation of emotionally intense material, creating a “safe space” where people will feel comfortable grappling with this intense material, discussing and offering techniques for making use of material from the MDMA-assisted session with particular attention in follow-up sessions to helping participants psychologically integrate the experience, and providing participants with recordings of MDMA-assisted sessions are all procedures or features of the therapeutic setting expected to support, enhance or stimulate the benefits of MDMA in combination with psychotherapy. By contrast, people who regularly consume “ecstasy” (material represented to be MDMA, often of unknown purity and dosage) do not typically experience improved psychological health (Lieb et al. 2002; Sumnall et al. 2004). Instead, these studies found an association between polysubstance use and psychological problems. While ecstasy use was not uniquely associated with these problems, using ecstasy didn’t mitigate these problems either. These findings, along with the previously described reports and studies suggest that the effects of MDMA are most beneficial when given within a psychotherapeutic context.

Ecstasy use in uncontrolled settings has been associated with serious adverse events, though these occur rarely (Baggott 2002; Gore 1999; Henry and Rella 2001). These include hyperthermia, psychological distress, liver problems, hyponatremia, and other events (Baggott et al. 2001). By contrast, MDMA produces only a slight increase in body temperature in controlled settings (de la Torre et al. 2000; Liechti et al. 2000), and to date, elevated blood pressure is the only adverse event reported during clinical trials (Mas et al. 1999; Vollenweider et al. 1998). Studies of the brain serotonin system in ecstasy users have reported reduced amounts of brain serotonin transporter in current repeated ecstasy users when compared with controls (Buchert et al. 2004; Reneman et al. 2001), and studies have detected impaired memory and executive function (planning and decision-making) in repeated ecstasy users (see for example Gouzoulis-Mayfrank 2000; Halpern et al. 2004; Wareing et al. 2004). Impaired cognitive function seems to be associated with heavy ecstasy use and may also be associated with use of other drugs (Halpern et al. 2004; Thomasius et al. 2003). Comparisons of brain serotonin and cognitive function made before and after up to two doses of 1.5 to 1.7 mg/kg MDMA failed to find reductions in cognitive function or in amounts of brain serotonin transporter (Vollenweider et al. 2000; Ludewig et al. 2003). As well, findings from at least some studies suggest that changes in serotonin transporter availability are transient (Buchert et al. 2004; Reneman et al. 2001) and specific to heavy users (Reneman et al. 2001). These findings suggest that the risks of a few doses of MDMA in controlled settings are considerably lower than seen after repeated use of ecstasy and other drugs in uncontrolled settings. If MDMA-assisted therapy can help people repair relationships damaged by emotional numbing and distancing and return to activities they have shunned because of their PTSD, then these minimal risks are counterbalanced by PTSD symptom reduction.

After reviewing previous accounts of MDMA-assisted therapy, we concluded that this treatment has promise for people with PTSD (Adamson 1985; Gasser 1994; Greer and Tolbert 1998; d’Otalora 2000; Widmer 1998). Therapists reported using MDMA to help patients confront and work with upsetting thoughts, feelings or memories while remaining relatively calm and clear-headed, and without eliminating emotional impact or inhibiting later recall (Greer and Tolbert 1998). The qualities that have been associated with MDMA in anecdotal reports (i.e. decreased defensiveness and enhanced therapeutic alliance) have the potential to be particularly useful in the treatment of this disorder. Subjective effects of MDMA reported in Phase I studies (e.g. Cami et al. 2000; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003;

Vollenweider et al. 1998), include positive mood, increased recall for emotionally intense material, and changed perceptions of meaning, may also hold significant roles in PTSD treatment. PTSD is a condition that involves prominent fear responses, social withdrawal, and distance from feelings (emotional numbing). Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value, and MDMA may facilitate this process. The sense of increased closeness to others, self-acceptance and interpersonal trust may help people with PTSD reduce social withdrawal and strengthen their social relationships or networks. Patients receiving MDMA-assisted psychotherapy can use the experience of increased self-acceptance and interpersonal trust as an alternative point of reference that can be carried over into everyday life. The combination of setting and pharmacological effects may help dissociate feelings of anxiety with intrusive thoughts or memories while at the same time increasing acceptance of unusual and disturbing somatic sensations as not necessarily threatening in and of themselves. Unlike other anxiolytic drugs, MDMA does not prevent or dampen emotions, nor does it interfere with later recall of the MDMA-assisted session. Furthermore, rather than eliminating anxiety altogether, previous reports and controlled studies suggest that MDMA produces moderate increases in anxiety with respect to losing control of oneself while reducing anxiety in response to emotionally upsetting thoughts or memories (Adamson 1985; Greer and Tolbert 1998; Vollenweider et al. 1998). The principal investigator is currently conducting a randomized, placebo-controlled, double-blind, sponsor-supported pilot study of two sessions of MDMA-assisted psychotherapy as part of course of 12 psychotherapy sessions in 20 individuals with treatment-resistant PTSD to test the safety and efficacy of MDMA-assisted therapy in this population. The sponsor will be supporting other studies of MDMA-assisted psychotherapy in people with PTSD to take place in Israel, Spain and Switzerland.

To summarize, MDMA is a psychoactive compound with a unique pharmacological profile that was previously used as a psychotherapeutic adjunct prior to being made illegal, and an examination of anecdotal reports and research studies, including the study currently being conducted by the principal investigator, suggest that the subjective effects of MDMA within a psychotherapeutic environment can serve to treat PTSD. This new intervention differs from the use of anxiolytics in psychotherapy, enhancing emotional experience and maintaining full recall of psychotherapeutic sessions. If further research confirms its safety and efficacy, MDMA-assisted psychotherapy may serve alongside other therapies as a means of treating PTSD.

Significance of the Proposed Study: There is currently no systematic, standardized formulation of MDMA-assisted therapy. Further research into the efficacy of MDMA-assisted therapy is hampered by the lack of standardized treatment. Specifically, conducting studies in larger samples or at several sites is not possible without a standardized model of the therapy or a means of training therapists to perform the standardized therapy. This project is intended to develop a treatment manual and accompanying measures of therapist adherence and competence that will allow for more thorough investigations of this innovative treatment. The completion of the treatment manual will support the long-term goal of conducting Phase III studies of MDMA-assisted therapy, and if findings continue to be promising, then these studies will lead to the development of another treatment option for people with PTSD.

C. Preliminary Studies

Investigators' Background and Experience: The principal investigator is the first psychiatrist to conduct a Phase II pilot study of MDMA-assisted psychotherapy in people with PTSD. Participants in this study receive twelve psychotherapy sessions, including ten 60 to 90-minute non-drug assisted psychotherapy sessions, and two six to eight-hour long experimental sessions with either 125 mg MDMA or placebo, with experimental sessions

scheduled three to five weeks apart. Twelve participants will receive MDMA and eight will receive placebo. This study now includes an open-label continuation for participants assigned to the placebo condition. Mithoefer and cotherapist Ann Mithoefer BSN have recorded all psychotherapy sessions to audio.

The principal investigator is a board-certified psychiatrist with ten years of experience treating PTSD. He has previously worked as an emergency physician and is a trained Holotropic Breathwork facilitator. Holotropic Breathwork refers to a non-pharmacological technique for inducing and working with altered states of consciousness (Grof 2000) largely based on Grof's work with LSD psychotherapy, making it similar to the approach used in the study of MDMA-assisted therapy in people with PTSD. He and Ann Mithoefer have had ten years of experience using Holotropic Breathwork with patients, including people with PTSD.

Other investigators include June May Ruse PsyD, Lisa Jerome PhD, Rick Doblin PhD and Elizabeth Gibson MS. Dr. Ruse is a clinical psychologist who has collaborated on earlier drafts of the treatment manual and has listened to session audio recordings. Dr. Jerome is a research associate working for MAPS with a background in social psychology who assisted in the initial stages of treatment manual development who will use her expertise on human MDMA research to inform the treatment manual, as well as offering editorial assistance. Dr. Doblin is president of MAPS, and Ms. Gibson is on the faculty of [college or university deleted] and edits a Holotropic Breathwork publication (the Inner Door). Both Doblin and Gibson are also certified Holotropic Breathwork facilitators. Dr. Doblin and Ms. Gibson will also offer editorial support during treatment manual development. She will continue to review and examine session material and collaborate on treatment manual development. Sherry Falsetti PhD, a psychotherapy researcher with a strong publication history, will act as a consultant and will be involved in treatment manual structure and design. Taken together the research team have authored or coauthored over 36 publications in peer-reviewed journals (e.g. Doblin 2002; Falsetti 2003; Freeman and Urschel (Ruse) 1997; Gamma et al. 2005; Mithoefer et al. 1972).

We (Dr. Mithoefer and Dr. Ruse) began developing a standardized treatment manual in 2002, assisted by research associate Lisa Jerome PhD and with financial support from MAPS. We laid the foundation of the manual with information drawn from literature detailing related psychotherapy models (for example Grof 2000), anecdotal accounts and case reports of MDMA-assisted therapy (for example Adamson 1985; d'Otalora 2000; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998), and Phase 1 trials of MDMA (for example Cami et al. 2000; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Pacifici et al. 2004; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider et al. 1998).
Once the pilot study of MDMA-assisted psychotherapy was underway, the team of investigators made use of observations from the study to inform the treatment manual draft, drawing on quotes and transcripts of recorded sessions.

The principal investigator has been instrumental in developing MDMA-assisted psychotherapy, and the Mithoefers and Ruse are familiar with procedures used in behavioral and treatment outcome research. Along with editorial assistance from Jerome, they have produced three editions of the treatment manual. Elizabeth Gibson has edited the most recent manual draft. The current draft of the manual addresses the introductory, MDMA-assisted and post-MDMA-assisted (or "follow up") sessions of MDMA-assisted psychotherapy. The current draft does not contain evaluative guidelines, and the investigators have not generated measures of therapist adherence or competency. Further, procedures for training of other therapists have not yet been developed.

Pilot Study Data: To date, seven participants have completed the course of the Phase II MDMA/PTSD study. None of the participants experienced serious, drug-related adverse events. Elevation in blood pressure and pulse occurred in all participants who received MDMA, but in no case were the levels dangerous and no participants required medical intervention. [Preliminary data and discussion of findings excised here and below.]

Difficulties inherent in maintaining the blind in placebo-controlled studies of psychoactive drugs raise issues concerning the impact that the placebo effect and experimenter bias may have had on study results, and the current sample size is small. [Additional text reviewing preliminary findings deleted.] These preliminary findings suggest that MDMA-assisted therapy can be safely performed in people with PTSD and that it reduces PTSD symptoms.

D. Research Design and Methods

Project Overview: This grant application is to support the completion of a manual of standardized treatment for MDMA-assisted psychotherapy. Treatment manual development will include the creation of evaluative guidelines, measures of therapist adherence and competence, and designing a program for training therapists in performing MDMA-assisted psychotherapy. The manual will be used to educate and train therapists who will conduct Phase III studies of MDMA-assisted therapy in the US. Phase III trials of MDMA-assisted psychotherapy in people with PTSD are part of a larger program to develop MDMA as a recognized psychotherapeutic adjunct. If necessary, the treatment manual will be altered to match any new findings in human MDMA research, including findings from the ongoing study. Completing the treatment manual will involve two years of work on the part of both investigators. Producing a treatment manual will involve continued examination and use of audio recordings of experimental sessions, as well as video recordings of non-drug assisted and experimental sessions. Both audio and video recordings will be examined and used in manual development. This grant will also assist in the development of treatment guidelines and measures of therapist adherence and competence. Treatment manual production will involve one or more meetings between the investigators and two research consultants. The project will be considered complete when the investigators have written a treatment manual, developed measures of therapist adherence and competence, and developed a means of training raters for these measures. The investigators will also begin designing a training program that will require the trainee to observe recorded or live MDMA-assisted psychotherapy and to demonstrate competence in performing MDMA-assisted psychotherapy, as assessed by the principal investigators.

Treatment Manual Development: The first phase of treatment manual development starts when the investigators begin making video recordings of both experimental and non-drug assisted psychotherapy sessions from the ongoing study of MDMA-assisted psychotherapy. The sponsor and the investigators will purchase and install equipment for making video recordings of psychotherapy sessions occurring as part of this ongoing study. Videorecordings will be made of participants already enrolled in the randomized, placebo-controlled study of MDMA-assisted therapy who give their written informed consent for session videorecording. The principal investigator will excise potentially identifying information and any segments the participant wishes removed from these recordings. All recordings will be sent to June May Ruse PsyD, who will view session recordings in their entirety. Dr. Ruse and the Mithoefers will strive to observe as many recordings as is feasible, but they may select specific recordings to optimize time and use of this information. Dr. Ruse will use these recordings to develop exemplars of therapy procedures. She will also note any variation in procedures

used across participants and across sessions, and differences between introductory, MDMA-assisted and follow-up therapy sessions, altering the manual accordingly. The treatment manual will build upon and integrate session observations into the text, using them as illustrative examples and as a means of better understanding and describing psychotherapeutic procedures. Any significant deviation from the procedures described in earlier drafts will lead to an alteration of the manual to reflect these actualities. Likewise, if examination of video recordings establishes the presence of procedures that are only performed during certain sessions during the course of therapy, the treatment manual and evaluative checklists will be written to reflect these details. Time needed for observing and examining video recordings is dependent upon the number of individuals who consent to session recording, and the extent to which open-label continuation sessions versus initial study sessions will be used. Six months will be set aside for viewing videorecordings, and six months will be used to edit and develop the manual. The second year will be devoted to refining the manual and developing evaluative guidelines for the treatment manual, and measures of therapist adherence and competence.

If examining sessions uncovers great variability in procedures employed across participants, the researchers will attend to these areas of difference and seek either to identify a common set of procedures or a rationale or decision tree for the use of different procedures, or they may detect areas of commonality between the different procedures. Though the investigators intend to rely mostly on recordings from the initial, placebo-controlled session, they will draw on recordings made of the open-label continuation of this study, referred to as “Stage 2,” recognizing that participants in this continuation have already developed some form of working alliance with the therapist-investigators and so these recordings may not adequately reflect processes occurring during the introductory phase of MDMA-assisted therapy.

During the process of manual development, the investigators will periodically confer with each other and with the research consultant. The investigators and consultant will discuss observations of session material and the investigators’ conclusions about therapeutic procedures, any new developments in human MDMA research, and a thorough on-site examination of the setting where the therapy takes place. At least two such meetings, each lasting no more than three working days, will be needed to organize, analyze and synthesize relevant information for treatment manual production. The end goal of each meeting is to arrive at a clearer understanding of MDMA-assisted therapy, with any later meetings specifically focused on editing the treatment manual to make it more accurate, concise and understandable. An investigator or research consultant will collect and save notes of these meetings for later reference.

The investigators will spend three to six months editing the treatment manual so that it is in line with observations from session recordings and any information gleaned from relevant reports and new research findings. Dr. Mithoefer, Dr. Ruse and Ann Mithoefer will have ultimate control over treatment manual structure and content, but they will be informed by the other co-investigators and the consultant. The meetings discussed above may fall at any period of time occurring after at least one editorial pass. If the investigators fail to reach a consensus or an understanding of the treatment manual during each meeting, then they will continue the discussion until they can produce at least a minimal consensus concerning the nature and structure of MDMA-assisted psychotherapy.

Developing Evaluative Guidelines: Once the investigators produce a manualized description of MDMA-assisted therapy, they will design evaluative guidelines for each standardized procedure, starting with assessment and screening and ending with study termination. The investigators will strive to produce concise and systematic

descriptions of each step in MDMA-assisted therapy. They will develop guidelines appropriate for use in training therapists unfamiliar with this therapy model. Up to two months will be spent developing guidelines for the treatment manual, with this process potentially occurring in parallel with treatment manual text development. Research consultants or other psychotherapists may assess guidelines for readability and ease of use, and the investigators will collaborate in editing the evaluative guidelines. Any disputes or conflicts over the guidelines content or structure will be settled during collaborative meetings between all investigators and the consultant. This aspect of manual development will be considered complete when the investigators have written a complete series of evaluative guidelines for each stage of MDMA-assisted psychotherapy.

Measures of Adherence and Competence: Dr. Mithoefer, Dr. Ruse and Ann Mithoefer BSN will discuss and generate measures of adherence and competence in treatment manual procedures for the use in training therapists for research studies, following models similar to those described by Carroll and Nuro (2002). These measures will be based on readily observable elements of standardized treatment. Measures of adherence and competence will become more specific and detailed if or when further research supports treatment efficacy. Dr. Jerome and Dr. Falsetti will assist in measure development, with Dr. Doblin providing additional editorial assistance if necessary. The investigators will take up to two months generating measures of adherence and competence. If necessary, the investigators may reserve videorecordings from at least one participant for use in testing these measures, with June May Ruse or another research consultant observing and rating the investigators on their performance of the therapy in each recorded session. This last step may not need to occur as part of this project, but may be performed if time permits. Once the investigators have designed a set of measures, they may train raters in the system of measurements. Raters may be other therapists familiar with the treatment manual contents or with MDMA-assisted psychotherapy.

Training Program: The investigators will devise a training program to teach therapists to perform MDMA-assisted psychotherapy for larger studies in the US either during or immediately after they have completed a satisfactory version of the treatment manual. The training program is likely to include observation of live or recorded MDMA-assisted sessions, reading the treatment manual, practice in session performance with feedback from the investigators, and possibly performance of an actual MDMA-assisted session.

Project Limitations: Limitations and difficulties of this project include potential difficulties resulting from study findings failing to demonstrate efficacy of MDMA-assisted psychotherapy in people with PTSD. Owing to small sample size and the exploratory nature of the ongoing study, the investigators would not halt treatment manual development if findings from the study the principal investigator is conducting failed to support reduced PTSD symptoms after MDMA-assisted psychotherapy. ~~However, if results from planned studies do not support the efficacy of MDMA-assisted therapy in people with PTSD, the investigators would halt treatment manual development.~~ However, even if studies find that MDMA-assisted psychotherapy is not efficacious, the treatment manual will still serve as a formal record of the procedures used during all research studies. The treatment manual could also serve as a starting point for reformulating procedures used in MDMA-assisted psychotherapy if the investigators believe that by doing so, they can improve treatment outcome. Difficulties in producing a coherent treatment manual may arise examining session recordings uncovers great variability in therapist behavior, or if the investigators find it difficult to produce or agree upon the content or structure of evaluative checklists or measures of adherence and competence. If the investigators conclude that there is too much variability in the performance of MDMA-assisted psychotherapy to develop a standardized treatment, then the investigators may change their frame of reference so as to allow for the observation and description of smaller or larger segments of therapy, or they may seek to establish at least one common element within each

stage of MDMA-assisted psychotherapy for use in designing a substantially revised treatment manual. The investigators will seek to resolve conflicts and difficulties in treatment manual and guideline development through continued dialogue and careful re-examination of the literature and observations of psychotherapy sessions. The same means of resolution described above will be applied to any difficulties in developing measures of adherence and competence. In addition, the investigators may request the assistance of another psychotherapist who will serve as an impartial reviewer and test case for the measures. Because four of the five investigators have worked together on previous treatment manual drafts, it is unlikely that difficulties in producing a treatment manual will arise, but if they do, they will be resolved through setting aside one recording from the current study or its open-label study continuation as a means of testing or examining one or more view of a stage, procedure or technique. If conflicts or difficulties cannot be resolved through any of the means described above, then the investigators may be required to make use of observations from planned research studies in the US. This would require the investigators to suspend treatment manual development until the arrival of the first recordings from a planned study. However, the investigators will exhaust all previous means of overcoming difficulties before deciding to defer manual development.

E. Human Subjects

Human Subject Involvement and Characteristics

Audio recordings and video recordings will all be of participants enrolled in an ongoing study of MDMA-assisted therapy in people with PTSD, with this study and all recording methods receiving approval from an IRB. Participants in this study are unpaid individuals, male or female, ages 18 through 70, who have been diagnosed with chronic posttraumatic stress disorder (PTSD) using DSM-IV criteria, with a score of 50 or above on the Clinician-Administered PTSD Scale (CAPS), a recognized measure of PTSD symptom levels. All participants must have failed to achieve remission of PTSD after at least three months of medication with a selective serotonin uptake inhibitor and at least six months involving at least twelve sessions of a recognized psychotherapeutic treatment. Aside from continuing to have significant PTSD symptoms after these treatments, all participants are physically healthy, as confirmed by detailed medical evaluation, and they cannot possess any contraindicating factors for the administration of MDMA. Because of the high co-morbidity of mood and anxiety disorders among people with PTSD (Faustman and White 1989), it is necessary to include individuals with these additional diagnoses (excluding bipolar affective disorder type I).

All participants must give written informed consent to having their study psychotherapy sessions video recorded in addition to consenting to take part in the study of MDMA-assisted psychotherapy in people with PTSD.

There are no additional inclusionary or exclusionary criteria for session videorecording.

Sources of Material

All participants' psychotherapy sessions, including experimental (MDMA or placebo-assisted) sessions are recorded to audio compact disk as part of the study protocol. As part of the proposed treatment manual and training development, video recordings will be made of all experimental and psychotherapy sessions in order to provide material for treatment manual development. Before using recordings in the context of this study, segments consisting of more than ten minutes of silence or inactivity will be removed from audio recordings,

and segments containing identifying information will be removed from both audio and video recordings whenever possible. In addition, participants can stop the recording of part or all of a psychotherapy session at any point in time during the session, and they can request that portions of the recording be excised at a later date.

Aside from their role as a potential element in MDMA-assisted psychotherapy, audio recordings are intended for research purposes only. Video recordings are intended for research use only. Recordings are intended to provide the investigators with a means of observing and analyzing psychotherapy protocols and samples from these recordings may be used as examples in the treatment manual. When this is done, all identifying or potentially identifying information will be removed from these recordings to maintain confidentiality. In addition the video recordings may be useful to those participants who request copies to review their sessions visually as well as with the audio recordings.

Participants sign forms for the release of information to any of the individuals who will need to obtain this information. Participants will sign a separate document indicating written, informed consent for the videotaping of experimental and non-experimental psychotherapy sessions.

Each recording will be identified only by the participant's initials on the source recording, and the participant's numeric identification on any copies of the recordings, as those supplied to the participant or to the psychotherapist. All audio and video recordings will be kept in a locked file drawer in a locked office. Other than the researchers involved in the treatment phase of the current MDMA/PTSD study and therefore, by necessity, know the participants' names, researchers with access to these recordings will not be provided with any information that would identify participants by name or by other means, such as social security number.

Removing identifying information from recordings and restricting access to researchers directly involved in treatment manual development will prevent the dissemination of confidential data, with or without identifying information. Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. While it is possible that individuals may be identified on audio or video recordings through means other than their names, such as through physical appearance or vocal timbre, restricting access to recorded material greatly reduces the opportunity for identification. Copies of recordings will not contain any personally identifying information, and will be identified by subject number only.

Potential Risks

Recording psychotherapy sessions poses a risk to participant confidentiality, and the procedure of recording psychotherapy sessions may increase participant distress or discomfort during the psychotherapy session. While this possibility certainly cannot be ruled out, it is our impression thus far that the procedure of audio recording sessions does not cause significant distress or discomfort, and the participants have reported that they soon get used to it and are not bothered by it.

Recordings contain a wealth of information about participants beyond dialogue or reference to the participant's name. People can be potentially identified by voice in audio recordings, and by appearance in video recordings, with appearance including facial features, clothing, gait or movements, or other features of the participant. It is possible that viewers could identify a participant through listening to or watching session recordings if they have had some prior contact with a participant, as through acquaintance or friendship.

Audio recording of experimental (MDMA or placebo assisted) psychotherapy sessions is an element of the study of MDMA-assisted therapy in people with PTSD. Participants in the study receive copies of these audiotapes and are encouraged, but not required, to listen to experimental session recordings. Because consent for audio taping is part of the initial study informed consent, the only alternative to making audio recordings of experimental sessions is for the participant to elect not to take part in the ongoing study. The same will not be true for video recordings. Making video recordings of psychotherapy sessions is necessary for treatment manual development, but is not required of participants taking part in the ongoing study of MDMA-assisted psychotherapy. The alternative to video recording is to decline to consent to having video recordings made of the session; participants can still take part in the study of MDMA-assisted psychotherapy while declining to have their psychotherapy sessions videotaped.

Participants may find the videotaping of psychotherapy sessions to be distressing or uncomfortable, either because recordings might lead to a breach in confidentiality or because they are uncomfortable with how they may appear to themselves or others in the recording. For most, the discomfort or distress related to video recording will be far smaller than the discomfort associated with psychotherapy or MDMA, but some people may be especially distressed by the prospective of having their sessions recorded.

It is also possible that awareness that their interactions with the investigators are being recorded may inhibit interactions between the participant and the investigators. Because audio recording is already included as part of the session protocol and because video recordings are required for producing a standardized treatment, the investigators must accept the potential alteration of interaction resulting from knowledge that a session will be recorded.

In writing the treatment manual, it is possible that the investigators may inadvertently provide enough information about a participant to render him or her identifiable. Such information might include details of the appearance, age or occupation of the participant, or details of traumatic event or events the participant experienced. Each individual descriptive element may not identify the participant when given alone, but if provided in biographical form, the information may contain enough details for others familiar with a participant to identify him or her.

Recruitment and Informed Consent

All recordings will come from participants enrolled in the study of MDMA-assisted psychotherapy in people with PTSD. Participants in this study are recruited through referrals made by physicians or psychotherapists, including referrals selected from among the patients of Dr. Mithoefer. Letters of referral specifically request the participation of crime victims experiencing PTSD symptoms, or people with a diagnosis of combat-related PTSD with a duration of no longer than five years. In addition, some participants are self referred, and in these cases permission is always obtained for the investigators to communicate with their psychiatrists and/or other therapists involved in their prior or ongoing treatment. Participants already enrolled in this study will be given additional consent materials relating to the videorecording of their psychotherapy sessions, and any prospective participants recruited after the investigators have begun to make videorecordings will receive two separate consent documents, one for participating in the study and one permitting recording of non-drug assisted and experimental psychotherapy sessions. Participants or prospective participants will discuss and review study procedures (including risks, potential benefits, and alternatives) before giving written informed

consent. The investigators will clearly differentiate participation in the study of MDMA-assisted therapy, including the open-label study continuation, and consent to the videorecording of psychotherapy sessions. We will accept no one who, because of illness, intelligence, language or cultural differences, appears unable to understand the nature and risks of the experiment, or who is unable to read and follow the informed consent or, if blind, is unable to listen to or follow the informed consent when it is read to him or her.

Protection of Human Subjects

The investigators will be attentive to any potentially identifying information contained on audio or video recordings, and they will remove any identifying information from these recordings if necessary, such as the full name of the participant or the full names of other family members or their exact street addresses. As described below, the investigators will make every effort to strictly safeguard the confidentiality of all participants. The investigators will also stop making a video recording at the request of the participant at any point in time during the psychotherapy session.

Original audio and video recordings for each participant will only be marked with the participant's initials and a numeric code for each participant, and all recordings will be stored in a locked file cabinet. Copies of recordings will only be marked with the numeric code randomly assigned to each participant. This will be true both of copies given to participants and copies given to the investigator examining and analyzing recordings during treatment manual development.

Potential distress related to the recording of study psychotherapy sessions will be dealt with through discussing the recordings with the participants. Participants and investigators will discuss the nature and purpose of the videorecordings prior to the onset of session recording. Understanding the purpose of making video recordings of sessions, reminding participants of the degree of control they have over what is recorded, and reassuring them that they are not required to watch themselves on video is likely to reduce or eliminate distress or discomfort in most participants.

When writing the treatment manual, the investigators will refer to individual participants as "Participant," by participant number (such as "Participant 2"), or by a pseudonym. The investigators will discuss any extensive use of biographical material with a participant before using it in the treatment manual. If a particular set of demographic and trauma-related details are perceived by the participant or the investigators as providing enough information for identifying a specific participant, then the investigators may confer with the participant about ways to reduce risk of identification. Means of reducing participant identification in the treatment manual include omitting key pieces of information about the participant or providing readers with false information about the participant's place of residence, occupation, or the nature of his or her traumatic event. The investigators will inform readers when they are using pseudonyms or when omitting or falsifying aspects of the participant's life in order to maintain participant confidentiality.

Confidentiality of Records

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Recordings of each participant's psychotherapy sessions will be identified only by the participant's initials on the original recording and by a numeric code on all copies of these recordings. Audio and video recordings will be kept in a locked file drawer in a locked office. Access to recordings will be limited

to regulatory agencies, researchers assessing the participant for changes in symptoms, and individuals analyzing data, and other therapists rating the investigators on their adherence to the manual. With the exception delineated above, researchers with access to recordings will not be provided with any information that would identify participants by name or by other means, such as social security number. If necessary, identifying information may be erased or otherwise removed from recorded material.

Participants will sign forms for the release of information to any of the individuals who will need to obtain this information.

Removing identifying information from recordings and restricting access to researchers directly involved in conducting the study or producing the treatment manual, unless a specific exception is agreed to in writing by the participant, should prevent the dissemination of confidential data, with or without identifying information. Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. While it is possible that individuals may be identified on audio or video recording through means other than their names, restricting access to these recordings greatly reduces the opportunity for identification of participants.

Potential Benefits of the Proposed Research To The Subjects And Others

Participants enrolled in the ongoing study are provided with copies of audio recordings of each experimental (MDMA or placebo-assisted) psychotherapy session, and the investigators encourage them to listen to these recordings as part of the therapeutic process. Video recordings of psychotherapy sessions will be available to participants upon request. It is possible that participants may benefit from viewing video recordings of their sessions, though this benefit is not an expected outcome of study participation. The participants do not receive any other material benefits from permitting the video recording of their sessions.

Producing a standardized manual for conducting MDMA-assisted psychotherapy will permit the training of therapists who will conduct Phase III studies in the US. These findings may demonstrate the efficacy of MDMA-assisted psychotherapy, and this would lead to the development of another treatment option for people with PTSD. Even if study findings are not as promising as preliminary data now appears, developing a treatment manual will provide investigators with a clear account of the psychotherapeutic procedures they performed. It is possible that retaining a record of therapy procedures from this study will allow the investigators to alter and improve treatment procedures in a manner that enhances treatment efficacy. Lastly, video recordings provide researchers with a wealth of information about observable behaviors that are not preserved in audio recordings, narrative accounts or psychometric measures, and these observations are not altered by biases possessed by the participant or the investigators, as might occur in retrospective accounts. The videorecordings used in these sessions will be the first extensive visual records of MDMA-assisted therapy. It is possible that these recordings will prove to be a resource for researchers interested in studying the nature and process of MDMA-assisted psychotherapy, and for researchers interested in the effects of MDMA on emotion and social interaction.

Importance Of The Knowledge To Be Gained

If MDMA-assisted therapy is found to be a promising treatment for reducing or alleviating the symptoms of PTSD, psychotherapists will want to learn more about how to conduct MDMA-assisted psychotherapy, and the

multi-site studies needed to further examine and confirm the efficacy of MDMA-assisted psychotherapy will require the existence of standardized procedures for performing MDMA-assisted therapy. Currently, information on the practice of MDMA-assisted therapy consists of anecdotal reports written prior to the scheduling of MDMA in the US or Europe (e.g. Adamson 1985; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998), and the results from one uncontrolled study that was not specific to studying the therapy in people with PTSD (Greer and Tolbert 1986). The current ongoing study is the first controlled, systematic investigation of the safety and efficacy of MDMA-assisted psychotherapy in a specific population, and the treatment manual under development will be the first of its kind. Crafting a set of standardized instructions for conducting MDMA-assisted psychotherapy is vital to progress in researching the efficacy of this potential treatment for PTSD. Even if study results fail to support the efficacy of this treatment, the treatment manual could be used to understand those results and to relate them to previous narratives and case studies.

Writing the treatment manual will provide the investigators with the opportunity to review and consider the nature and structure of MDMA-assisted psychotherapy. Understanding how MDMA-assisted therapy is conducted in this specific patient population is liable to make it easier for the investigators and other researchers to apply this therapy to other populations of people with PTSD, as those whose PTSD arose from vehicular accidents, natural disasters, or life-threatening illnesses. It is also possible that writing the treatment manual will lead the investigators to improve and refine the stages of MDMA-assisted therapy in response to observing recorded sessions or re-evaluating study findings in the context of assessing consistency, adherence and competence of therapy performance.

The recordings the investigators will use to develop the treatment manual will be the first extensive record of MDMA-assisted therapy in people with PTSD, and this information is not equivalent to Phase I trials or anecdotal accounts of MDMA-assisted psychotherapy. Raw observations could be used to test hypotheses about the nature or structure of MDMA-assisted therapy or about the effects of MDMA on one or more specific observable behaviors. The treatment manual could serve as an aid in developing other related treatment manuals, as for the population of people experiencing anxiety as a result of advanced stage cancer. Investigators with access to a treatment manual detailing standardized procedures will be better able to point to similarities and differences between the use of MDMA in one condition, such as PTSD, and its use in another, such as cancer-related anxiety. More generally, the information contained de-identified transcripts of recordings and in the treatment manual could inform disparate areas of psychology and neuroscience, including clinical psychology, psychopharmacology, and social psychology. Researchers interested in therapist-patient interactions during psychotherapy, in the effects of MDMA upon behavior or emotion, and on other drug-specific or setting-specific behaviors could use the raw observations, transcripts of the observations or the treatment manual to test hypotheses about these areas of investigation. Use of the treatment manual or transcripts of the recordings used in treatment manual development would prove valuable even if further research fails to support the efficacy of MDMA-assisted therapy in people with PTSD.

Inclusion of Women and Minorities

Both men and women are eligible for participation in the ongoing study, without preference given to either gender. It is possible that there will be more women participants because PTSD arising from crime victimization is higher in women than in men. Women participating in the study must not be pregnant or lactating, and they must be using an effective means of birth control during the course of the study to avoid inadvertent prenatal exposure to MDMA. All participants have their experimental (MDMA or placebo-assisted)

sessions recorded to audio compact disk. The investigators will make video recordings of all consenting participants, whether male or female, without preference for either gender.

Members of all ethnic or racial categories are eligible to participate in the ongoing study, without preference given to any race or ethnic group. It is anticipated that the racial/ethnic composition will be close to that of the regional population. Since the ongoing study is in 20 participants, it seems likely that not all racial/ethnic groups designated by the NIH will be represented in the proposed study. As noted above, audio recordings are made of experimental therapy sessions for all participants. The investigators will make video recordings of all consenting participants, without preference for any particular racial or ethnic group. Because video recordings will occur in an even smaller sample of participants enrolled in this pilot study, it is unlikely that the racial or ethnic composition of participants consenting to the videorecording of their psychotherapy sessions will be representative of the regional or national population.

Targeted/Planned Enrollment Table

See “Targeted Enrollment form” on p. 42

Inclusion of Children

Individuals between the ages of 18 and 70 are eligible to participate in the ongoing study of MDMA-assisted psychotherapy that will provide material for developing the treatment manual. Individuals who are unable to give adequate informed consent will not be enrolled in this study, including all individuals considered to be minors by the state of South Carolina. To date, there is insufficient information concerning the effects of MDMA-assisted therapy in adults with PTSD, therefore the FDA will not allow the study to be open to children under the age of 18. As noted above, audio recordings will be made of the experimental sessions of all participants, and video recordings will be made of psychotherapy sessions for all participants who consent to the recording of their sessions. s. We will attempt to show no preference in relying on material from participants of any given age group included in the study.

Data and Safety Monitoring Plan

All recordings used for treatment manual development, and any extensive transcripts of the recordings, will be stored in a locked file drawer in a locked office at the offices of Michael C Mithoefer MD, and copies of recordings sent to the other investigator will be stored in a locked file cabinet at the offices of June May Ruse PsyD. Recordings of experimental sessions will be edited to remove any identifying information prior to use as material for working on the standardized treatment manual. Participants will be identified by number and initials only in case report forms, and by number only in any computerized data. Access to recordings used in manual development will be restricted to investigators evaluating the sessions, though participants may receive copies of their own sessions for their review. Identifying information will also be removed from these recordings.

Data Safety Monitoring Board

The ongoing study that will provide the investigators with observations and examples for the treatment manual is a small pilot study, and no multi-site studies are proposed in this application. However, the sponsor employs a data safety monitoring board (DSMB) to assess the study of MDMA-assisted psychotherapy in people with PTSD. The DSMB is composed of three individuals, at least one of whom is a psychiatrist and another a

psychotherapist with expertise in PTSD. The DSMB has meetings scheduled periodically to assess the safety of participants in the study of MDMA-assisted therapy. They report their recommendations as to whether the study should be continued as is, modified, or halted to the sponsor, the IRB and the FDA. They will also meet to review serious adverse events. The DSMB may discuss audiotaping and videotaping of psychotherapy sessions, but their main concern is the safety of MDMA-assisted psychotherapy as performed in this study.

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Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Treatment Manual Development for MDMA-assisted therapy f

Total Planned Enrollment: 20

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	9	9	18
Ethnic Category: Total of All Subjects *	10	10	20
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	5	5	10
Racial Categories: Total of All Subjects *	10	10	20

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

Principal Investigator/Program Director (last, First, Middle): Mithoefer, Michael C.

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ REVISION of application number: _____

(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

☐ COMPETING CONTINUATION of grant number: _____

(This application is to extend a funded grant beyond its current project period.)

☐ SUPPLEMENT to grant number: _____

(This application is for additional funds to supplement a currently funded grant.)

INVENTIONS AND PATENTS *(Competing continuation appl. and Phase II only)*

☐ No ☐ Previously reported

☐ Yes. If "Yes," ☐ Not previously reported

☐ CHANGE of principal investigator/program director.

Name of former principal investigator/program director: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved: _____

☐ SBIR Phase I ☐ SBIR Phase II: SBIR Phase I Grant No. _____ ☐ SBIR Fast Track

☐ STTR Phase I ☐ STTR Phase II: STTR Phase I Grant No. ☐ STTR Fast Track

1. PROGRAM INCOME ***(See instructions.)***

All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
1/01/06-1/01/08	$0.00	

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***

In signing the application Face Page, the authorized organizational representative agrees to comply with the following policies, assurances and/or certifications when applicable. Descriptions of individual assurances/certifications are provided in Part III. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

•Human Subjects; •Research Using Human Embryonic Stem Cells• •Research on Transplantation of Human Fetal Tissue •Women and Minority Inclusion Policy •Inclusion of Children Policy• Vertebrate Animals• •Debarment and Suspension; •Drug- Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)*; •Lobbying; •Non-Delinquency on Federal Debt; •Research Misconduct; •Civil Rights (Form HHS 441 or HHS 690); •Handicapped Individuals (Form HHS 641 or HHS 690); •Sex Discrimination (Form HHS 639-A or HHS 690); •Age Discrimination (Form HHS 680 or HHS 690); •Recombinant DNA Research, Including Human Gene Transfer Research; •Financial Conflict of Interest (except Phase I SBIR/STTR); •Smoke Free Workplace; •Prohibited Research; •Select Agents •STTR ONLY: Certification of Research Institution Participation.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☐ DHHS Agreement dated: _____ ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with In process Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	50,000	x Rate applied	25.00	% = F&A costs	$	62,500
b. 02 year	Amount of base $	50,000	x Rate applied	25.00	% = F&A costs	$	62,500
c. 03 year	Amount of base $		x Rate applied		% = F&A costs	$	
d. 04 year	Amount of base $		x Rate applied		% = F&A costs	$	
e. 05 year	Amount of base $		x Rate applied		% = F&A costs	$	
					TOTAL F&A Costs	$	125,000

*Check appropriate box(es):

☐ Salary and wages base ☐ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

Appendix to Grant Application

Treatment manual development for MDMA-assisted therapy
PAR-03-108
NIH SMALL RESEARCH GRANT PROGRAM (R03)
Mithoefer, Michael C, principal investigator

Summary of appendix contents:

A) Comparison of Therapeutic Approaches for Treating PTSD – with tables

B) Data from first seven subjects in current pilot study of MDMA-assisted psychotherapy for treatment resistant PTSD

C) The following published reports regarding PTSD, MDMA or psychotherapy manual development:

1) Bradley et al. 2005
2) Cami et al. 2000
3) Carroll and Nuro 2002
4) Doblin 2002
5) Greer and Tolbert 1986
6) Harris et al. 2002
7) Liechti et al. 2001
8) Lester et al. 2000
9) Tancer and Johanson 2003
10) Vollenweider et al. 1998

D) "MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder. A Revised Teaching Manual Draft" Please find posted on the following URL:

http://www.maps.org/research/mdma/ptsd_study/treatment-manual.html (HTML)

http://www.maps.org/research/mdma/ptsd_study/treatmentmanual.pdf (PDF)

Printed copies are available upon request.

E) Consultant Curriculum Vitae: Sherry Falsetti PhD