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RE: MDMA-Assisted Psychotherapy for the Treatment of Post Traumatic Stress Disorder

Dear Dr. Wells:

We (Rick Doblin, Ph.D. and Michael Mithoefer, MD) have reviewed your letter of January 3, 2003 to Dr. Rick Doblin, in which you asked us to respond to a number of issues that arose during your IRB panel's review of our protocol. We welcome the opportunity to respond, and to make improvements in our research design as a result of your input. We agree that credibility is particularly important in controversial areas of research such as this, and that a good working relationship between our research team and the IRC, based on mutual respect, is crucial to our efforts to appropriately address the many complex and sometimes conflicting needs that must be considered.

We will respond below to the issues you raised in the order in which they appear in your letter:

“Potential for harm to human subjects from MDMA”

We are including as a separate document an update to our comprehensive review of the published, peer-reviewed scientific literature on MDMA, which we submitted to FDA in October 2001. We are also submitting a CD with PDF copies of 165 scientific papers published after the original review along with a few older papers referenced in the updated review. We have also included in our review some recent and still unpublished Phase I and Phase 2 clinical data that several researchers have been willing to share with us for submission to the IRC-IRB. In short, these newer papers and reports increasingly

provide data that tends to strengthen in several ways our original conclusion that the risks of the administration of two doses of 125 mgs of MDMA to human subjects in the context of our protocol are minimal and can be ethically justified.

We agree that there is cause for caution about the cumulative effects of repeated doses of MDMA based on retrospective studies of recreational "Ecstasy" users (with "Ecstasy," referring here to material represented as MDMA but not infrequently containing other substances). While studies in Ecstasy users continued to find subtle and selective impairments in memory and executive function, findings were not consistent across all studies (e.g. Bhattachary and Powell 2001; Fox et al. 2001a; Fox et al. 2002; Morgan et al. 2002). Furthermore, one research team failed to find impaired memory in Ecstasy users, and reported that verbal intelligence and concurrent cannabis (marijuana) use were more closely associated with lower memory scores than Ecstasy use (Simon et al. 2002).

Fortunately, controlled human research over the last 15 months has demonstrated that concurrent marijuana and amphetamine use and other confounds call into question the role of Ecstasy in the neuropsychological and memory findings that have been reported in some Ecstasy users (Daumann 2001; Morgan et al. 2002). Epidemiological research has shown that mood disorders in frequent Ecstasy users most often precede the use of MDMA and indeed are predictive of that use (Lieb 2002). Primate research has demonstrated that even massive serotonin reductions are not associated with cognitive impairment, with the primates needing to be challenged with another drug before showing even minor differences on only 2 out of 6 tests (Taffe 2002) . Furthermore, the research over the last 15 months has continued to demonstrate the importance of the role of temperature in contributing to the risks of MDMA (Darvesh et al. 2002; O'Shea et al. 2002;Yuan 2002). Data from people who primarily use Ecstasy recreationally, often involving extended dancing in hot environments, are thus likely to provide an overestimate of the risks of a moderate amount of pure MDMA administered on two separate occasions within a clinical, temperature-controlled setting with pre-screened volunteers.

In addition, we are reassured by the fact that recent Phase I studies in the US and Europe, using MDMA doses that often have exceeded 125 mgs have looked for and failed to find evidence of psychological or neuropsychiatric toxicity, or any lasting physiological toxicity to any organ system, and have been conducted without a single serious acute adverse effect. As discussed in the Investigator's Brochure, researchers in Switzerland have failed to find differences in serotonin transporter binding measured at baseline and one month after up to two doses of MDMA (Vollenweider et al. 2001). Additionally, a forthcoming publication by the same team has also failed to find any changes in cognitive function after MDMA administration in a drug-naïve sample (Vollenweider, In Press).

"The study design might not be sufficient to yield evaluable results"

> *"…it was suggested that the basic revised protocol should be limited to ten pages. Alternatively, please consider a comprehensive abstract or summary."*

In response to this request, we are including a five page summary of the protocol as a separate document. We will respond below to the specific questions you raise in this section:

> *"There are, perhaps three variables being examined instead of the desired single variable."*

The committee appears to misunderstand three aspects of the proposed study. We will clarify these first before responding to this comment:

- We will not be doing any Holotropic Breathwork with study participants.
- Bodywork is not an independent variable but one of the non-drug elements of this treatment approach, as described in the treatment manual. It will be used in both control and experiment subjects if appropriate, probably rarely.
- We are using only instruments that are already validated.

The only factor that will vary between the two groups is the MDMA. Nevertheless, we certainly agree with you that any study involving drug-assisted psychotherapy is bound to be more complex and challenging than a simple drug study with regard to standardizing treatment variables.

> *"The evaluation of outcomes was unclear. …how will you know when the question has been answered?" "Although this is a study of the effect in PTSD, the condition did not appear to be well defined.…nor, in fact, did the criteria demonstrate how the diagnosis of PTSD was being made"*

Our primary outcome measure is the Clinician Administered PTSD Scale (CAPS). This well validated scale is broadly used and accepted among PTSD researchers (Schnurr 2002, Weathers 2001). It is the instrument that was used in the clinical trials of sertraline (Zoloft) and of paroxetine (Paxil) that led to their FDA approval for PTSD. The CAPS allows an interviewer, in a standardized way, to determine whether or not the subject meets DSM IV criteria for chronic PTSD, which are the criteria we are using to make the diagnosis.

A fifteen point decrease (improvement) in the CAPS scores can be taken to indicate clinically significant change in an individual subject 's symptoms (Weathers et al 2001). However, we do not expect to be able to definitively answer any question about efficacy with this study. Since this will be the first controlled study in the US with this patient population, it is of necessity a small, Phase II pilot study. Our goal is to gather preliminary evidence about safety and efficacy in this patient population in order to determine whether to proceed to conduct a subsequent small study to standardize the therapeutic method, develop the treatment manual and associated objective checklists, and generate data for the possible design of larger, Phase III studies that would have the biostatistical power to definitively answer questions about safety and efficacy.

"The rationale for selecting PTSD instead of any of the several equally involved diagnoses was not clear."

We're not exactly sure what you meant by "equally involved diagnoses" since in the patient population we seek to treat, comorbid disorders will be present in some but not all subjects. We attempted to explain our rationale for focusing on patents with PTSD as our required diagnostic category in the protocol section on pages 5-7 entitled "Rationale for Studying PTSD". We will list below what we think are the key points:

- anecdotal and uncontrolled studies with PTSD patients suggest potential
- subjective effects of MDMA decrease fear and defensiveness, increase empathy and self-acceptance, properties of special importance in traumatized PTSD patients
- subjective effects of MDMA may enhance therapeutic alliance
- PSTD is a serious and expensive mental disorder and public health problem, with an 8% lifetime prevalence in the general US population,
- a sizable percentage of patients suffer treatment-resistant chronic symptoms persisting ten years or more (Kessler 1995)
- Controlled trials of existing FDA approved drug treatments for PTSD have demonstrated a response rate of between 53% and 62% and a six-month relapse rate among responders of 5% with continued drug treatment and 26% without maintenance drug therapy. (Brady 2000, Davidson 2002, Marxhall 2001)
- Recent reviews of psychosocial treatments for PTSD report average symptom reductions ranging between 40% and 80% across studies (Foa 2003).
- These data indicate that some patients are quite well served by existing methods while, for many people, currently available treatments are inadequate.

- The most common comorbid conditions appear to be major depression, followed by generalized anxiety and substance abuse (Montgomery et al. 2000). While it would be quite interesting to study MDMA-assisted psychotherapy for these conditions at some time in the future, there are several reasons, listed below, for our choosing to focus on PTSD.

- There is evidence that PTSD generally precedes most comorbidities, particularly affective and substance abuse disorders (Kessler et al., 1995. Both this evidence and clinical experience provide some rationale for thinking of PTSD as the "underlying" disorder (Schnurr et.al, 2002) in many patients and deciding to direct research toward it in particular.

- PTSD is a disorder for which psychotherapy remains a mainstay of treatment. This is less true of mood and anxiety disorders, which are now commonly treated with an emphasis on drug treatment and relatively less emphasis on psychotherapy. A recent issue of The Journal of Clinical Psychology was devoted to an update of outcome research into PTSD treatments. Several statements from one of the articles support

this stance, "Most promising of the tested drugs are the anti-depressants, although the effects of these drugs on PTSD are comparatively modest in relation to their effects on depression and panic. … Because of the complexity of symptoms and problems typically displayed by victims of trauma, drug treatment alone never can suffice to alleviate the suffering associated with PTSD. … In general, psychotherapy tends to be much more widely practiced and studied than is pharmacotherapy…" (Solomon 2002, p. 955, 948) Since our study includes a considerable amount of psychotherapy and is designed to study MDMA's potential for catalyzing the psychotherapeutic process, it seems preferable to study a disorder for which psychotherapy plays an important role in treatment.

- In subjects with active substance abuse the risk of relapse during the study leading to possibly dangerous drug-drug interaction between MDMA and abused drugs would be of concern. For this reason, we have elected not to study this group

- .*"The eligibility criteria did not differentiate any level of PTSD in terms of severity, duration, symptoms or extent of prior care… the members strongly suggest limiting the subject population to those who are most severely impaired by PTSD."*

We agree that the greater the severity of the PTSD, the greater the risk that can be tolerated in the experimental treatment, especially in treatment-resistant patients. However, as analyzed in our initial literature review and in the updates submitted with this application, we think the scientific evidence demonstrates that there is only a minimal risk that any of our subjects would suffer clinically significant physiological harm from two doses of 125 mgs of MDMA administered in our clinical setting.

Regarding psychological harm, the risks seem greater the more severely impaired is the subject. It is important to balance the intention to avoid risk to people with only mild problems with the desire to avoid accepting patients who are at significant risk for self-harm or who would not tolerate tapering off psychotropic medications.

Since this is an initial exploratory study, we felt it appropriate to include subjects with a range of PTSD severities in order to gather the most information. Nevertheless, we do understand and appreciate the committee's concerns. We therefore propose we add the following stipulation to the protocol:

- Inclusion criteria would require a score of 50 on the CAPS. This would be intended to eliminate subjects with only mild symptoms. Although the CAPS has been validated as a research tool, proposed severity ranges have not been. Weathers states that, "Five rationally derived severity score ranges for interpreting CAPS total severity scores have been proposed and are currently being evaluated. The range for "moderate" PTSD is 40-59 (Weathers 2001).

Another measure of the severity of PTSD is related to a subject's lack of responsiveness to currently available treatments. We therefore offer below a specific proposal regarding the amount of prior treatment subjects must have received prior to being eligible to

participate in this study: The discussion below also serves as a response to part of section "4" on page 3 of your letter,

> *"The history or efficacy of various psychodynamic approaches to PTSD are essentially ignored.")*

- Prior treatment (which must have failed to resolve symptoms to below a CAPS score of 50) must include both a trial of an SSRI lasting at least three months and psychotherapy lasting at least six months and including at least twelve psychotherapy sessions in the course of treatment.

In deciding on the definition of "psychotherapy" for the purposes of these criteria it is important to consider the current state of knowledge as expressed in several recent reviews.

> "….there is no singular treatment of choice for PTSD."
> "the appropriateness and effectiveness of any given strategy may depend on several factors… there exist relatively few systematic studies of efficacy for many of the treatment approaches practiced" (Shea 2002, p. 871,875)
> "Treatment should be tailored to the severity and type of presenting PTSD symptoms, the type of trauma experience and the many likely comorbid diagnoses and adjustment problems."
> "…contemporary views emphasize the need for a flexible, integrative approach to treatment in order to deal with the complex and varying needs of individual trauma victims." (Solomon 2002, p. 947, 958)

We will add the requirement that only therapies for which there exist controlled trials indicating efficacy will qualify as prior psychotherapy. There are three such categories:

1.Cognitive Behavioral Therapies

This group includes such treatments as exposure therapies, cognitive reprocessing, EMDR and anxiety management approaches (Soloman 2002). Resick and Schnicke have reported a reduction of PTSD symptoms in rape victims with a program of 12 weekly group sessions of Cognitive Processing therapy. (Resick 1992). Jaycox and colleagues from the University of Pennsylvania, describe a treatment for PTSD used at the Center for Treatment and Study of Anxiety in Philadelphia consisting of 9 – 12 ninety minute individual sessions of Cognitive –Behavior Therapy. (Jaycox 2002). There have been at least twenty controlled trials of EMDR treatment for PTSD, fourteen of which have been in civilian populations. (Shapiro 2002) Typically, 12 or fewer sessions are used. The International Society for Traumatic Stress Studies has designated EMDR as efficacious for PTSD (Chemtob et al. 2000)

2.Insight Oriented Therapies

This group includes psychodynamic therapy and hypnotherapy. Krupnick, at Georgetown University describes a 12 session model of individual psychodynamic therapy for adults with PTSD, based on methods originally developed by Horowitz. Krupnick states that there have been two controlled studies of psychodynamic therapy for PTSD, one of which included a hypnotherapy group. Improvement was seen with both psychodynamic therapy and hypnotherapy compared to controls. (Krupnick 2002)

3. Stress Inoculation Training

A stress inoculation training program of 9 sessions over 5 weeks including relaxation training, controlled breathing, positive imagery, cognitive restructuring and distraction techniques led to a 55% reduction in PTSD symptoms. This was slightly better than prolonged exposure in the immediate follow-up and slightly less than the benefit from prolonged exposure at 3 months. (Foa 2003)

"*Please comment on why you elected to dose at this level by subject rather than by weight."*

About half of the Phase I studies conducted with MDMA have administered fixed doses, while the other Phase I studies have used a mg/kg dosing schedule. Though it may still prove to be the case, there is no clear evidence demonstrating that the amount of MDMA that crosses the blood/brain barrier is substantially and/or proportionally affected by bodyweight. Furthermore, psychiatric drugs in general are not typically administered primarily on a mg/kg basis. Sensitivity to MDMA, as with other psychiatric drugs, is likely to vary more due to psychological factors than to weight.

We have chosen to administer a standardized dose of 125 mgs, but have specified in our exclusion criteria a subject weight range (50 -105 kgs) that is designed to keep the mg/kg dose within the range of 1.2 - 2.5 mg/kg. While we expect body weight to have some impact on metabolic factors, the literature suggests that 125 mgs can be safely administered all across our weight range. We also believe that a standardized dose of 125 mgs is more likely to result in subjects receiving a therapeutically appropriate dose than if we were to use a dose standardized on mg/kg. This view is based in part on anecdotal reports and case histories about the therapeutic use of MDMA, and in part after noting the wide range of doses administered in prior Phase I studies that used mg/kg dosing, often in amounts substantially exceeding 125 mgs. For example, in Dr. Tancer's report on his latest Phase I study, which used mg/kg dosing schedules, doses ranged from 52 to 171 mgs, with nine of twenty-four doses exceeding 125 mgs (Tancer, personal communication). In the 2 mg/kg condition, there was a 67.2 mg difference between the lowest dose administered (104.6 mg) and the highest (171.8 mg).

“Reliance on medical model – Insufficient concern about psychiatric components”

> *"The measures described to handle either emergent or chronic psychological harm were considered insufficient…"*

We strongly agree about the importance of this aspect of patient safety. We realize from your comments that, although the treatment manual (See Ruse et al. 2002, pp. 13-14) describes in some detail specific methods for supporting difficult emotions, we have not made the specific provisions for handling psychological destabilization explicit enough in the protocol.

Before going into our proposals for correcting this deficiency in the protocol, we would like to offer some further perspective about this subject. We believe the possibility of destabilization exists with all methods of therapy for PTSD, and that this is widely recognized and accepted by researchers and clinicians alike. Solomon and Johnson, in their review of psychosocial treatments for PTSD, discuss the possibility of complications such as "exacerbation of depression, relapse of alcoholism and precipitation of panic disorder." They point out that "A major challenge for all of these treatments is that of balancing the patient's need to confront the trauma with the risk that such exposure will re-traumatize the individual. Research suggests that exposure must be long enough in duration for the response to extinguish (90 minute sessions are recommended)…" This paper also emphasizes the therapeutic value of techniques that carry a risk of destabilization by virtue of their ability to stimulate deep emotional processing, and that being able to safely manage that risk is probably an essential element of treating PTSD. Solomon and Johnson underscore the importance of "establishing trust and maintaining a good therapeutic relationship, explaining the importance of retelling the story or otherwise revisiting the traumatic experience, clarifying expectations, including potential short-term exacerbation of symptoms". They express a point of view that is very much in keeping with our approach when they state that, "…(PTSD therapy) typically involves the need to overcome avoidance of external and internal cues that trigger memories of the trauma by providing a safe environment in which the person can re-experience the event without becoming retraumatized. Some form of sustained emotional processing of the trauma memory appears to be essential to the effective treatment of PTSD, regardless of technique" (Solomon 2002, p. 948). It is our hypothesis that the effects of MDMA will facilitate this process and possibly decrease the likelihood of psychological complications, but we must certainly be prepared to handle any psychological complications that may arise.

As a team of therapists, Dr. Mithoefer and his wife, a psychiatric nurse, have had extensive experience supporting and working with patients with PTSD. They have more than ten years of experience supporting PTSD patients through challenging emotional work and dealing with the destabilization that sometimes occurs. They use both EMDR, which is essentially a form of exposure therapy, and Holotropic Breathwork, which produces intense experiences much like those we expect with MDMA. When applying both of these treatments, they take very seriously and pay close attention to the possibility of temporary exacerbations of symptoms and even of potentially dangerous destabilization, and they have considerable experience in successfully dealing with these eventualities. Providing proper support and affect management or "stress inoculation"

techniques to balance the uncovering and abreactive work is an essential element of any therapy for PTSD that aims at confronting the trauma in a way that can provide deep healing.

We respond below to the committee's request for a more specific set of procedures for the management of emergent or chronic psychiatric complications of treatment. These new proposals are in addition to the existing provisions in the protocol; screening out subjects that appear to be at risk for suicide or self harm; providing support through 24-hour therapist availability by phone, and the option of additional psychotherapy sessions and/or "rescue medications" if needed. We propose:

- All subjects will be required to have a partner, family member or friend who will be with them for at least 24 hours after each treatment session. The subject will be required to allow this person to meet with him/her and the therapists at the end of each MDMA session and will be given the number to reach Dr. Mithoefer 24 hours a day. (Prior to this the presence of a support person had been optional)

- If a subject is anxious, agitated, in danger of any self harm or is suicidal at the end of the 6 – 8 hour MDMA/placebo session, the therapists will remain with the patient for at least two more hours. During this time, the therapists will employ the affect management techniques described in the manual, will talk with the subject to help him or her gain cognitive perspective of their experiences, and will help them implement the self soothing and stress inoculation techniques they were taught in the introductory sessions. If this situation should occur at the end of one of the ninety-minute follow-up sessions at least one of the therapists will be available to stay with the patient for at least two additional hours.

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

  A. A psychiatric nurse, therapeutic assistant or therapist (whose availability we will have arranged ahead of time) , will stay with the patient until the time of his or her appointment with the study therapists the next day. The therapists will then meet with the subject daily until the period of destabilization has passed. At any time during this process, Dr. Mithoefer may make the clinical judgment to proceed to option B.

  B. Hospitalization for stabilization

For those subjects engaged in an on-going therapeutic relationship, we will actively involve their outside therapists in the management of any psychiatric complications of treatment. In the event of such complications we will engage in a more frequent and scheduled series of communications with these therapists, as discussed below in the section responding to your concerns about possible conflicts with current therapists.

"Advertising and recruitment…"

We will forgo any advertising or other recruitment other than letters to therapists. These letters will be sent to psychiatrists and other psychotherapists in Charleston, SC and surrounding communities within a four hour drive of Charleston. If we are not able to recruit enough subjects with these letters, we will submit a proposal to the IRC requesting approval of other methods of recruitment.

"…a broad sample of people call and are screened by telephone. What screening tool is used at that point?"

We have written a script for screening during the initial phone contact and have submitted it as a separate document.

"…the members strongly recommend raising the minimum age"

You raised the concern that young people with PTSD could be considered a specially vulnerable population, implying either that fully informed consent would be more difficult to obtain in young people and/.or that the treatment would be riskier in these subjects. Regarding the issue of informed consent, we note the increasing emphasis placed by the National Institutes of Health on including young people in clinical research. This suggests that it is possible to obtain fully informed consent from subjects under the age of 21. Regarding the question of the risk of the treatment to young people, we believe it is entirely possible the risk would be lower in young people than in older subjects and also that the closer in time MDMA is administered to the initial trauma, the greater the chance of a successful treatment. Nevertheless, we understand the sensitivity of this issue. We therefore offer to raise the minimum age to 21.

"The history or efficacy of various psychodynamic approaches to PTSD are essentially ignored."

This is addressed above in the response to question 3 on page 2 of your letter asking about *"the extent of prior care"*.

"the impact of prior psychiatric treatment."

The fact that all subjects will have participated in at least one specified form of non-drug psychotherapy will likely put them in a better position to safely tolerate and benefit from our treatment. By virtue of the inclusion criteria, the prior therapy will have failed to lower the CAPS score below 50. The pharmacological treatment that must precede study participation is discussed earlier in reference to eligibility criteria.

"conflict with current therapists…" and *"this study relationship is bound to alter the prior relationship. This should be carefully handled in conjunction with the prior therapist….In addition, for those subjects already in therapy, this study*

relationship is bound to alter the prior relationship. This should be carefully handled in conjunction with the prior therapist"

We appreciate the level of the committee's insight into the issues at hand indicated by these concerns. Dr. and Mrs. Mithoefer face challenges in this regard on a regular basis when patients are referred by other therapists for Holotropic Breathwork or EMDR. It is important that participation in the study not undermine an existing therapeutic relationship with an outside therapist. We look upon outside therapists as potentially valuable allies in our efforts to provide psychological support for subjects during the study and to identify any potential subjects who fit exclusion criteria numbers 8 or 9 (8 - Patients who would present a serious suicide risk or who are likely to require hospitalization during the course of the study; 9 - Patients requiring ongoing concomitant therapy with a psychotropic drug). We already require subjects to give Dr. Mithoefer permission to talk to any psychiatrists, other therapists and any prescribing physicians. Subjects are permitted to continue outside therapy at the same frequency as before the study. We will now add the following:

- Potential subjects who are in treatment will be required to discuss the study with their therapist before agreeing to take part in the study. Dr. Mithoefer will be required to contact their therapist and prescribing physician (if they are on medications) to discuss issues of safety before accepting a patient into the study. If a subject is not currently in treatment, Dr. Mithoefer will be required to talk to their former therapist and physician (this last requirement will be waived only if the therapist or physician is no longer reachable for a reason such as no longer being in practice).

- Dr. Mithoefer will contact each subject's therapist after each MDMA/placebo session to inform them about the patient's experience and any therapeutic gains or potential problems. He will also let them know that he will call them about any significant developments between MDMA/placebo sessions.

- Dr. Mithoefer will give each outside therapist his emergency number and ask the therapist to call if they are aware of any problems developing, have any questions about what we're doing, or have any insights they think would be helpful to us.

- Patients may make session tapes available to their therapist if they wish.

"The desire to prevent drug interaction needs to be evaluated in terms of the potential destabilization of the patient for the good of the study…"

This is a central concern in every pharmacological study in PTSD patients. This issue has been addressed in the same manner in all such FDA-approved studies by the required withdrawal of all other psychiatric medications. Similarly, maintaining the washout requirement is essential to this study. Serotonin reuptake inhibitors, frequently employed in the treatment of depression, directly block or attenuate acute effects of MDMA by

competing with MDMA for the serotonin transporter (Liechti et al. 2000), and administering MAOIs concurrently with MDMA could increase the risk of hypertensive crisis.

Since comorbid disorders often follow the initial trauma that produces PTSD, there are also potential therapeutic advantages in withdrawing patients from medication designed in part to reduce the symptoms of these comorbid disorders. MDMA-assisted psychotherapy involves bringing difficult emotions to the surface in a safe and supportive context in order to facilitate abreaction, catharsis and integration. An increase in symptoms that may follow withdrawal from psychiatric medications for comorbid disorders, while presenting a therapeutic challenge that must be managed carefully, can also provide an opportunity for greater access to the benefits of both the drug and the non-drug components of our treatment approach. Subjects in both the MDMA and the placebo group may benefit from the increased emotionality that may occur as a result of the withdrawal of psychiatric medications.

We have made provisions for frequent evaluation of subjects' emotional status, and, in the previous section on management of possible psychiatric complications, have delineated our methods of handling any such complications. These provisions will allow us to provide the clinical monitoring and support necessary to allow safe withdrawal from psychotropic medications and the enhanced therapeutic potential that may result.

We will take care to screen out any subjects who appear to be at significant risk for destabilization. It will not serve the interests of the subjects or the study if we accept patients who turn out to be unstable and must be dropped from the study to be returned to other medications. In addition, the study therapists will be seeing the subjects for a 90 minute session the day following each MDMA/placebo session and again every week subsequently. During these visits they will be monitoring for signs of destabilization or relapse of co-morbid conditions. They will also be available by pager at all times, and subjects and their support person and outside therapist, if any, will be encouraged to call the PI immediately if there are signs of destabilization or relapse. With this level of monitoring and support, we believe the risks posed by tapering off medications are manageable. Since these subjects are suffering from significant PTSD that has not responded to other treatment, we believe the potential for benefit is such that there is a favorable risk/benefit ratio.

> *"…confounding of experimental results if subjects are destabilized prior to study evaluation."*

We're not sure how the withdrawal of subjects from psychiatric medications, which may or may not be associated with destablization, would confound the experimental results. The withdrawal of psychiatric medications would occur equally to subjects in both experimental and control groups. Some subjects might score worse on initial measures after withdrawal than they would have prior to withdrawal, but outcome measures would be administered to all subjects after withdrawal. Perhaps there will be symptom changes in either direction for some patients after medication withdrawal, however, since subjects

will be randomized to either the experimental or control group, these possible fluctuations are not likely to confound the experimental results. The withdrawal of subjects from other psychiatric medications in the Zoloft and Paxil trials seemingly did not confound experimental results in those studies. In any case, we are not seeking to generate definitive findings in this study but simply to gather pilot data about safety and efficacy of the use of MDMA-assisted psychotherapy in our patient population, during which for the reasons we have explained above concurrent medication is contraindicated.

> *"…the distinction between doctor-patient relationship and subject-study investigator relationship in psychotherapy."*

In both the doctor-patient relationship and the subject-study investigator relationship the primary responsibility of the PI is to safeguard the safety, rights and welfare of the patients/subjects. The Belmont principles of "respect for persons", "Benificence" and "Justice" to which a study investigator must adhere are quite similar to the ethical principles governing a doctor-patient relationship. There are, however, several ways in which these relationships differ. If a physician's patient does not want to have enough information to constitute detailed informed consent, the physician may make the judgment to proceed with a treatment anyway at the patient's request. An investigator may not do so. The investigator must ensure that the subject has read, understood and carefully considered and signed the informed consent before allowing that subject in the study. In addition, although a physician has a responsibility to allow any patient to withdraw from treatment, a study investigator has a particular responsibility to be sure a subject is only continuing in a study at his or her own discretion. An investigator must not to allow a subject to continue if there is reason to believe he or she is being unduly influenced. In psychotherapy this may be particularly challenging because transference feelings and the resulting possibility of unconscious coercive influences are likely to be more powerful. An investigator doing psychotherapy must be alert to these influences and be prepared to explore them with subjects and to exercise good judgment about whether or not a subject is psychologically able to make an independent decision about participating in a study. Further, an investigator has a moral fiduciary relationship with a subject that requires him or her to minimize conflicts of interest.

Conflicts of Interest

> *" Dr. Mithoefer is recruiting from among his own patient base. Although this would be effective, it provides a substantial conflict….Influences which might be appropriate in one setting can become undue influences in another…"*

We agree that this does provide a potential conflict that must be handled carefully. We believe it can be handled and that the advantages of including Dr. Mithoefer's patients (better basis for making judgments concerning suitability for safely participating; existence of an already established therapeutic alliance) make it worthwhile to take measures to manage the conflict. It will be important for Dr. Mithoefer to be mindful of this conflict and to make every effort to minimize any effects his bias might have on recruitment or selection from among his patients. He must emphasize to any potential

subjects the fact that if they should decide not to participate or if they do not turn out to meet criteria, or if they participate but for some reason do not complete the study this will not effect his willingness to continue treating them. He must explore carefully with them any fears or other feelings they have about this. In addition, we will add to the protocol the following outside monitoring of the informed consent process in any of Dr. Mithoefer's patients who are considering participating in this study:

> - Any potential subjects who are or have been patients of Dr. Mithoefer within the last three years must have a 30 minute meeting with another psychiatrist at the sponsor's expense, to discuss the decision about whether or not to participate before signing the informed consent. This psychiatrist will have veto power over a patient's participation, to be exercised if the psychiatrist thinks there is undue influence. In addition, any subjects from Dr. Mithoefer's patient base will meet a second time with this psychiatrist between the first and second MDMA/placebo sessions to ensure that they remain unencumbered by undue influence over whether or not to continue in the study.

> *"In addition, of course, is the potential (perceived or real) of selection bias if Dr Mithoefer is selecting among his own patient population."*

Dr. Mithoefer will certainly select those patients whom he believes are likely to do well in the study. Since we will be recruiting by means of a letter to other therapists, asking for suitable referrals, the same will presumably be true of therapists providing referrals as well. FDA guidelines encourage subject selection based on criteria most likely to generate positive responders to treatment. The main concern that we must keep in mind is not to overgeneralize the results of this study to the wider universe of PTSD patients who do not meet our selection criteria In addition, it should be remembered that each potential subject must meet all criteria for inclusion and exclusion and that most selection criteria for participation do not rely on the therapist's judgment.

> *"The investigators are the intervenors who are also completing some key assessments."*

This is actually not the case. All assessments will be performed by Mark Wagner, PhD. He is a hired consultant, is not involved in any interventions and is blind to what occurs during therapy and to which subjects are in either the experimental or control groups.. This is stated on page 16 of the study protocol.

> *"An external statistician should be hired to review the results."*

Dr. Wagner, though a clinical psychologist, rather than solely a statistician, is very experienced in statistical analysis, as a review of his CV will demonstrate. He is the external statistician who will be hired to analyze and review the results.

> *"The DSMC should be far more independent."*

It is standard practice at the Medical University of South Carolina here in Charleston for the PI to be on the DSMC. We propose to add to the DSMC a third physician who is not otherwise associated with the study. We believe there is an advantage to Dr. Mithoefer's remaining on the DSMC because he will have first hand information about what transpires during study sessions. The two other physicians would, together or independently, have a mandate to report any concerns to the IRB and to the FDA even if Dr. Mithoefer were not in agreement.

We hope the above has satisfactorily addressed the committee's questions and concerns. We look forward to further communication with you, including the opportunity to meet with the committee in person on January 28. Please let us know if there is any additional information you would like prior to our January 28 meeting

Sincerely,

Michael C. Mithoefer, MD

Rick Doblin, Ph.D.

References: (The following list includes any references referred to above that were not already listed in the protocol submitted to the IRC.)

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