February 4, 2003

Rick Doblin, Ph.D.
President, MAPS
3 Francis Street
Belmont, MA 02478-2218

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

Dear Dr. Doblin:

During the IRB meeting January 28, at which both you and Dr. Mithoefer were present as guests, the members reviewed your latest response, dated January 20.. After you left, the members discussed the remaining issues at length, and decided once again to return the application for more information.

The members greatly enjoyed meeting you and Dr. Mithoefer. We asked many questions, and gained more insight into the study goals and limitations. The overall impression was that Dr. Mithoefer is an extremely dedicated and responsible clinician, and that you are enthusiastic, well informed, and earnest in your approach. These are all very positive qualities, however, they increased our level of discomfort about the most confounding element of running this study—the inevitably profound and pervasive bias of those who will control how the data in this design is collected, interpreted, and disseminated.

This very long letter will attempt to address the remaining substantive issues, and to mention some of the specific areas of the protocol that must be made concrete and understandable before any approval can be considered. There are a many issues presented here, and some new ones may not be known until some issues are explained in greater detail. Therefore, our letter may be hard to follow; for which we apologize in advance.

Conflict of Interest

Given that conflicts of interest are often manageable, we tried to focus on ways that this protocol, which has some indication of benefit to society, could be conducted in a way that best limits the influence of ardent, well-meaning bias. The conclusion was simple. Since MAPS has a significant level of funding, this project should be ***turned over to an independent third party***. We recognize your deep involvement in this project, but are concerned that it will render the study scientifically untenable and the results justifiably quite vulnerable to skepticism.

1. To be specific, we would like you to arrange for this study to be conducted by a CRO (or similar professional organization) that is experienced in psychological research. Our staff is looking at available options, but we urge you to begin your own search. Please let us know what options you find; the IRB would like to evaluate the credentials of candidate organizations before the final choice is made.

2. To lend further objectivity and credibility to the study, there should be a second investigational site—preferably chosen by the CRO. The two sites may then enroll up to 10 subjects each, and any subject who drops out or is withdrawn after the first MDMA (or placebo) session will count towards enrollment. The IRB will want to be notified of all drop-outs or withdrawals within 24 hours, so that the reasons can be evaluated and monitored.

3. The study should be conducted with the highest practicable degree of scientific rigor. The inter-site comparison will help to monitor the degree of reproducibility. However, we will be most interested to hear of the provisions for monitoring by your CRO, and would like you (and them) to design a one-page monitoring report that can be faxed to the IRB after each session is completed.

   All deviations from protocol that occur during the sessions should be disclosed on these monitoring reports, and for significant deviations, we will reserve the right to suspend study activity at any time, until satisfactory plans for preventing re-occurrence have been approved by the IRB.

Protocol – Study Design Issues

Naturally, we will want to review a revised protocol that incorporates all the excellent safeguards and new procedures that you offered in response to our first letter. There will also need to be significant changes as a result of this letter. When all is said and done, there should be one document of less than 20 pages, with a few brief appendices. The protocol layout should resemble in simplicity and clarity the excellent 4-page summary provided in your most recent response.

1. The IRB would like to evaluate the validity of the CAPS instrument ***for this study,*** as there seems to be some ambiguity. When asked at the meeting how a patient who scores 50 might present clinically, Dr. Mithoefer responded that the CAPS "is not well validated," but your January 20 letter assured us that you "are using only instruments that are already validated." Although we are certain that these statements conflict only in context, we would like to review the instrument, as well as any evidence of its validity for this use.

2. Your verbal response at the meeting to our questions about the drug manufacturing and testing process was satisfactory, however, we would like you to provide us with a one-page summary description.

3. Similarly, please provide us with a brief summary of the DEA licensing progress. Final approval will not be possible until all necessary licenses are obtained.

4. We would like to review copies of all letters from the FDA regarding their review of this protocol.

5. Some of the members are still uncomfortable with the bodywork element—on two different levels. First, it introduces the opportunity for a variable, despite your assurance that it is equally possible for either the active drug or placebo group. The bodywork is not standardized; it is intended to be done in response to need. Second, it is not applicable to the goals of the study. Its intent is purely therapeutic, and not related to the evaluation of MDMA-assisted psychotherapy. In fact, the reluctance of you and Dr. Mithoefer to abandon this therapeutic element is a major concern for the board, and reinforces their perception that there are non-scientific goals desired from the sessions. Please specifically eliminate this variable from the protocol, or present us with a standardized, highly justified alternative..

Protocol – Safety Issues

1. The members remain very concerned about agitated subjects, or those with suicidal ideation associated with study procedures. In your January 20 response, you tried to justify the risks as being similar to those inherent to "all methods of therapy for PTSD." That is not the point. The point is that this is ***research***; not therapy, and any research-related risks must be minimized. Your suggested safeguards were readily accepted, but the board would like to see even more protections. Please expand your plans to respond to these situations, taking the following points into consideration:

    a. Any agitation or adverse reaction must be reported by telephone to the IRB within 24 hours, with a follow-up written report from the DSMC within five business days.

    b. The "partner, family member, or friend" who will "be with (all subjects) for at least 24 hours after each treatment (sic) session" will need to be recruited, consented, and educated. Please provide all the necessary revisions and new documents for review.

    c. Your plan to have the therapists "remain with the patient (sic) for at least two more hours" needs more clarification. We presume you will not detain someone against their will. The ultimate option—hospitalization—is always available, but how will the investigators (not "therapists") deal with a person who was agitated, but presents stability? As we indicated to you at the meeting, there could be some kind of relapse hours, or even days later. This critical safety concern will need considerable specificity and strengthening. You present MDMA as a "catalyst," so how will you control the safety of the post-catalytic reaction?

As an aside, the use of the words "treatment,""patient," and "therapist" throughout your protocol, consent form, and responses are contributory towards the perception that treatment is desired. There can be no treatment implied or expected from what amounts to a Phase I pilot study! As you said in your January 20 letter, "…this is an initial exploratory study." Please take pains to transform all these subliminal references to more acceptable scientific terms that will dispel critics and inspire confidence in even the most hardened skeptic.

2. We welcome the addition of a third DSMC member, and concede that Dr. Mithoefer's involvement will be helpful. Your astute decision to provide the two other members with veto power over Dr. Mithoefer demonstrates a level of understanding about regulatory monitoring that is encouraging. Please provide us with copies of the current professional licenses and *curriculum vitae* of the other two doctors.

3. It would probably be a good idea for subjects to carry a wallet card that would identify them as study participants in case of an unexpected drug screen. Please design one with Dr. Mithoefer's 24-hour number on it, and submit a copy of the text for review.

4. It's probably overkill to ask for the qualifications of the EMT team that each site will employ, but we would like at least to know the name and phone number of their company.

5. The blood sodium tests will be transported to an outside laboratory, presumably late in the day. How soon will the test results be available? How will subject confidentiality be protected during transport of the specimen and transmission of the results?

6. Another seemingly trivial but practical issue is the care and feeding of study subjects. As they will be fasting when they arrive, what food and drink will be provided during the all-day sessions? (They should probably be screened verbally for food allergies.)

<u>Recruitment & Consent Issues</u>

The recruitment of subjects from the practice of Dr. Mithoefer was seen as problematic, due to the possibility of inadvertent coercion. The members were most impressed with his professional manner and forthrightness during the meeting, and his clinical dedication to his patients seems exemplary. However, the members perceived in him an understandable tendency to look at the conduct of this study through the colored lenses of desire to provide therapeutic benefit The subconscious, subtly slanted language in your written materials reinforces our concern, as we have said before. Let us discuss the issues further, because they are extremely important:

1. You said in your response that, "Dr. Mithoefer will certainly select those patients whom he believes are likely to do well in the study." This could be interpreted as those who will tolerate study procedures well, or those who might be expected to benefit from the therapeutic interventions that are part of the study. Given our first-hand, favorable impressions of Dr. Mithoefer as a responsible, dedicated clinician, we tend to believe the latter. This is a selection bias, and it must be managed.

   Your excellent and generous provision to pay for an evaluation by an objective psychiatrist to determine if potential subjects have made an autonomous decision is a very good place to start. However, this might not reveal a therapeutic misperception on the part of the patient or the doctor. One way to reduce selection bias would be to randomize selection of potentially eligible subjects. This could be done as simply as tossing a coin. We trust you are able to devise some way to mitigate this significant bias. (This is not yet a demand of the IRB; we wish to hear your input.) Skeptics and critics of the study will certainly zero in on this area of the protocol.

   How do you plan to train or orient this "veto psychiatrist"? We urge that this key individual be an established researcher.

2. Regarding potential subjects who are referred by other therapists, we will need to re-review the letter submitted with your original submission, once all the information about recruitment is available. Similarly, we defer judgment at this time on the telephone recruitment script. We are certain you can appreciate our desire for circumspection.

3. The consent form will likely be the last document to be finalized. It is an epic document already, and we see more information that could be added, based on some of the issues brought up in this letter. Is there a way that it could be broken into digestible pieces? The information on risks of MDMA, for example, could be redesigned into a pamphlet. The goal is not to overwhelm a potential subject, but to enroll qualified individuals into the study. This is most easily done by avoiding the college textbook approach. Look at an eighth grade textbook, and admire the clarity, type size, graphics, and white space. The goal is to facilitate ***understanding*** as well as fostering a fully informed decision. When the time comes, our staff can be of great assistance to you in designing materials that will avoid "Post-Traumatic Consent Disorder."

<u>Personnel</u>

As you probably expected, we will want to review the qualifications of all the key players in this study—at both sites. A search of your already voluminous file has not produced a copy of Dr. Wagner's *c.v.* or license. Please provide another copy of each. Likewise, we will want to review the qualifications of the "veto psychiatrist" when he/she is selected.

Documentation & Privacy

As an appendix to the protocol, we will need to review all forms that will be used for this study, including those for data collection, screening, reporting of adverse events, etc. The information to be collected should support only the stated goals of the study.

1. It seems that a study-specific release form will be needed to allow the exchange of information between Dr. Mithoefer, referring therapists, and other involved professionals. It would probably be most effective if it briefly described the study, and provided specific descriptions and limitations of the information to be exchanged. Please provide a draft for review.

2. We hope, at this point, that you have heard of HIPAA[1] before. This new regulation will apply to any research subjects enrolled after April 14, 2003. At a minimum, your research sites will need to obtain authorization from the study subjects to disclose private health information to outside entities (to us, to you, to other study doctors, etc.). If HIPAA comes as a surprise, you have our sympathy. Our "draft" information packet is attached for your information.

In Closing

We would like to emphasize a few general, but important points at the end of this long letter:

1. No approval of this study by our IRB is implied or promised at this point. We are still evaluating if this project is feasible from a human protections standpoint. We are also attempting to maximize the scientific benefit, and minimize the risks of undertaking this study.

2. The final protocol and appendices will be expected to be a concise, succinct, **single** document.

3. We reserve the right to bring up new issues at any time that new information becomes available to us. We trust you will be patient with us if we seem redundant, or if we ask for something you have already sent. The review of this study has already consumed reams of paper, and there will certainly be more deforestation to come.

4. The information in this letter should not be posted, summarized, or otherwise inferred on your web site (or other public releases of information). You may report publicly that a response was received from IRC, and that review continues. To exceed our stipulated limitations on this issue will jeopardize our relationship, which at present we think is collegial, professional, and mutually respectful. Please honor our requirement for privacy.

[1] Health Insurance Portability and Accountability Act

We look forward to receiving eight (8) copies of your response and of any revised or new materials. For any revisions that are made, please indicate them or provide an index to the changes, and include a new version date on the revised copy. When these documents have been received at our office, they will be distributed for the next available IRB meeting. If you have any questions or objections to any of the above, please feel free to call our office.

Sincerely,

James L. Bauer, M.D., IRB Vice-Chair
(by) Don Mayne, CIP, IRB Director