Independent Review Consulting, Inc.
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January 3, 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 meeting of January 2, 2003, the IRB reviewed your new application. The members voted to return to you with multiple questions and to defer a decision pending your responses.

To set the stage for the multitude of questions that follow, several general points were accepted.

- Many beneficial drugs are accompanied by substantial side effects.
- Although there is a potential for significant harm to subjects, this study also has the potential for significant benefit to future patients and for future work in this field.
- In this arena, more than in most others, credibility at all junctures is critical.
- A working relationship between the IRB and MAPS will require mutual respect and acknowledgement of the conflicting needs among subjects, patients, science, ethics, politics and our culture.
- In line with this, on our part, the board agreed that great differences develop, the board will inform MAPS immediately so as not to waste further resources for you or for us.

POTENTIAL FOR HARM TO HUMAN SUBJECTS FROM MDMA

The known and theoretical risks of this drug are a core question. If the risks are as significant as some would argue, it is unlikely that the benefit derived from even the most polished study would be merited. Thus our first task is to assess the potential for harm.

You produced a very excellent and broad literature review. The reviews are thorough, yet they end with summaries which slant interpretation towards “caution” about extrapolating the results of a given small single study to possible general Ecstasy effects – rather than the usual interpretation of such studies individually and in the aggregate as pointing toward caution about likely cumulative adverse effects of even small doses. It seems clear that there are increasing signs of harms being reported to which we must pay attention.

It is important that the last year and a half of work is not reflected in your summary. The members asked for a current summary.

THE STUDY DESIGN MIGHT NOT BE SUFFICIENT TO YIELD EVALUABLE RESULTS

One comment echoed by multiple members was that you seem to have taken a rather easy study and added so much to it that it was no longer practical. Certainly, we presumed that with each review you have had, with each consultant you have consulted, and with each rave that is reported, you added to it and filled in corners. The members recommended a return to your basics. In fact, it was suggested that the basic revised protocol should be *limited to ten pages*. Alternatively, please consider a comprehensive abstract or summary.

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Although you can have appendices, this should be a simple and tight study that is easily described.

1. There are, perhaps, three variables being examined instead of the desired single variable. The first variable, of course, is the MDMA. The second seems to be the body work element along the lines of the Grof Transpersonal Therapy. Third, the "Holotropic Breathwork" was added. Although each of these may be ultimately interesting or important, they cannot all be assessed in this one study. In addition, you mentioned the need to evaluate some of the instruments. Did we misread this? Given the number of already validated instruments, there should be no reason to include further variables.

2. The evaluation of outcomes was unclear. The changes being sought may be subtle and difficult to measure. In biostatistics, the more difficult it becomes to see a difference, the more subjects are needed. You are seeking only 20 subjects. What is the outcome you are seeking and how will you know when the question has been answered?

3. Although this is a study of the effect in PTSD, the condition did not appear to be well defined. The rationale for selecting PTSD instead of any of several equally involved diagnoses was not clear. The eligibility criteria did not differentiate any level of PTSD in terms of severity, duration, symptoms, or extent of prior care, nor, in fact, did the criteria demonstrate how the diagnosis of PTSD was being made. Given the risks and benefits, the members strongly suggested limiting the subject population to those who are most severely impaired by PTSD. Further information on how you would define PTSD-related eligibility was required.

4. The dose is set at 125 mg/person. Please comment on why you elected to dose at this level by subject rather than by weight. Based on the literature, first, and on your experience, is there any safety or metabolic difference by weight?

RELIANCE ON MEDICAL MODEL –
INSUFFICIENT CONCERN ABOUT PSYCHIATRIC COMPONENTS

Much of your concern about potential harms seemed to center on medical harms. (Please note that this is a very common bias in all drug studies.) This study, however, by its nature has many psychosocial elements as well that were not as well addressed.

1. The measures described to handle either emergent or chronic psychological harm were considered insufficient given that, by definition, these are people who are destabilized by their PTSD in the first place. Much more attention to evaluation and care or this aspect is required. Please note that the instructions concerning treatment of side effects is predominantly medical (and could be summarized in about 10 lines) rather than being more balanced between medical and psychosocial.

2. Advertising and recruitment using flyers and referrals is common in medically based studies. In this case, however, it did not seem appropriate. Would advertising elicit people fitting the criteria? Where would it be circulated to work effectively? Letters seeking referrals are also suggested. What group of people would receive the letters? The

recruitment seems to be very general in tone so that a broad sample of people call and are screened by telephone. What screening tool is used at that point? Is there a script? What information is recorded?

3. Eligible ages also seem medically rather than psychologically or socially determined. Certainly subjects over 18 are legally eligible. There is substantial concern, however, that "young" people with PTSD who, perhaps, have been through a variety of negative experiences since their original crisis, can easily be considered to be a vulnerable population. Given this, the members strongly recommended raising the minimum age.

4. The history or efficacy of various psychodynamic approaches to PTSD are essentially ignored. The approach begins and ends with modern assumptions of chemical psychiatry. Failure of prior treatment, seems to mean failure of SSRI's. The impact of prior psychiatric treatment, the conflict with current therapists, and the alternatives that should precede use of MDMA should be included.

5. The design calls for a wash-out of psychiatric medications and herbal supplements. This seems particularly onerous especially for the placebo group. 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 and the confounding of experimental results if subjects are destabilized prior to study evaluation.

6. The use of MDMA is as an adjunct to psychotherapy, is very dependent upon a good doctor-patient relationship. Although you discussed some of it, please delve into the distinction between doctor-patient and subject-study investigator relationships in psychotherapy. 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.

CONFLICTS OF INTERESTS Although there are some pure researchers who have no vested interest at all in the outcome, most investigators have a bias going into a study. Conflict of interest is common; the management of potential conflicts between interests is crucial. Not surprisingly, everyone involved in MAPS shares a common value system regarding the use of MDMA. Your management of that bias and conflict was under-developed.

1. Dr. Mithoefer is recruiting from among his own patient base. Although this would be effective, it provides a substantial conflict. His patients already owe an allegience to him. Unlike a diabetic patient recruited by their physician, his patients are psychologically more susceptible to influences. Influences which might be appropriate in one setting can become undue influences in another especially where instability and vulnerability are involved. In addition, of course, is the potential (perceived or real) of selection bias is Dr. Mithoefer is selecting among his own patient population.

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2. The investigators are the intervenors who are also completing some key assessments Those people asked to evaluate outcomes and to monitor sessions are all involved somehow in desiring a positive study result.

Study credibility will be vastly enhanced by including external evaluators in several places. For instance, the DSMC should be far more independent. There are a multitude of independent clinical monitors, some of whom specialize in psychiatric studies, who could act as blinded evaluators. An external statistician should be hired to review the results.

There were a number of other comments raised although many are likely to be resolved in a re-write and others can wait to see if, given what is said above, you wish to continue with this submission. Certainly revision and comments about the consent document will need to wait until the (hopefully simpler) protocol is ready.

The members all noted that they sincerely hope that we can, together, find a design that will produce credible and useful results without subjecting the human participants to undue risk of harm.

We look forward to receiving eight copies of :

- A response letter
- Protocol of 10 pages or less
- Supplement to literature review
- Plan for external evaluation

When they are received they will be circulated, once again, to the full board for their review at a convened meeting. At the time that the response is scheduled for review, we invite you to join us for discussion either by phone or in person. If you have any questions or objections to any of the above, please feel free to call our office.

Sincerely,

Penny Wells, Dr.P.H., IRB Chair
(by) Erica J. Heath, MBA, President IRC