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Ms. Erica Heath
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RE: MDMA-Assisted Psychotherapy for the Treatment of Post Traumatic Stress Disorder

Dear Erica,

I'm writing to inform you of some actions that MAPS has undertaken in response to Dr. Bauer's letter of February 4, 2003, and to share with you some initial responses to a few of the issues that were raised in his letter. Eight copies of a longer and more detailed letter will follow in week or two.

We understand and appreciate that your review is an ongoing process with the possibility of new issues arising at any time. Once we start the study, there will be a flow of new data that will also necessitate continual reevaluation. We look forward to working with you in close collaboration with whatever data reporting schedules you request.

Two new issues raised in Dr. Bauer's letter have to do with avoiding bias in the collection of data. To that end, the panel recommended that a CRO take over the project, and also that the study be split in two and conducted at two different sites with two independent teams.

Engaging the services of a CRO and conducting multi-site studies are excellent suggestions that MAPS intends to implement if and when we are able to conduct Phase III studies. However, these suggestions seem premature in our first Phase II study, as I will briefly discuss below. While I am pursuing in good faith a bid from a CRO for data monitoring, I do not feel that such services are needed to ensure reliable data that is scientifically tenable and able to withstand skeptical analysis.

<u>CRO MONITORING</u>

On Wednesday, February 5, I spoke with Loren Miller, Ph.D., Vice President, Regulatory and Scientific Affairs, PPD Development, the clinical research (CRO) operating

subsidiary of PPD (ppdi.com), a "leading global provider of discovery and development services and products for pharmaceutical and biotechnology companies…with more than 5200 employees in 24 counties." Dr. Miller works out of the PPP Development office in Research Triangle Park, Morrisville, NC., reasonably close to Charleston, SC where Dr. Mitheofer's study will take place. Dr. Miller is developing a bid for a minimal system of data monitoring for Dr. Mithoefer's study, with the bid expected in about a week. Dr. Miller has already indicated that the bid will be in excess of $20,000, perhaps substantially so.

I was first introduced to Dr. Miller in the early 1990s, through my interactions with FDA's Pilot Drug Evaluation Staff (PDES), the group that regulated research with Schedule I drugs. Dr. Miller had written articles about the PDES, which FDA officials had given me. In 1999, MAPS brought Dr. Miller to Israel for our MDMA research conference, so that he would have an opportunity to learn about all the clinical research around the world being conducted with MDMA. Though MAPS benefited from his participation in the meeting, the bill for educating him about MDMA convinced me that MAPS could not afford the services of a CRO. When discussing the IRB request, Dr. Miller observed that CRO monitoring of research is much more important for Phase III trials than for preliminary Phase II pilot studies.

DR. MARK WAGNER'S EXPERTISE AND PROCEDURES

As noted in Dr. Bauer's letter, the IRB panel has not had the opportunity to review the CV of Mark Wagner, Ph.D., the consultant in charge of screening and outcome measures. Dr. Wagner was not chosen for this position because of any prior relationship with MAPS, or because he believes in the value of MDMA-assisted psychotherapy, or because he was a friend of Dr. Mithoefer's. Rather, Dr. Mithoefer contacted Dr. Wagner because of his professional expertise in administering screening and outcome measures, as you can see in the CV which was sent via email to Mr. Don Mayne earlier today. Among other responsibilities, Dr. Wagner is Director of Neuropsychological Services, Department of Neurology, Section of Neuropsychology, Medical University of South Carolina and serves as a Peer Reviewer, Journal of Traumatic Stress, 1998–Present.

Dr. Wagner will conduct the screening and outcome measures in a manner that renders him blind to which experimental group the subjects are in. This is standard operating procedure for the conduct of FDA-approved clinical research. This approach serves as an adequate and appropriate method of resolving the issue of biased data collection for studies sponsored by pharmaceutical companies, which are at least as vulnerable to concerns about bias as MAPS. Dr. Wagner will be sending you a letter within the next week or two to introduce himself to the IRB panel and explain his procedures to reduce or eliminate bias in measurements.

DATA MONITORING AND FDA COMPLIANCE BY MS. AMY EMERSON

In addition to the data gathering work of Dr. Wagner, document tracking, data management and monitoring and FDA compliance issues related to this protocol will be

supervised and conducted by Ms. Amy Emerson, Clinical Research Associate, Chiron Corporation, a biotechnology pharmaceutical company located in Emeryville, CA. (Pharmaceutical). As her resume (attached) states, Ms. Emerson has expertise in the management and monitoring of large Phase 1-III trials. While Ms. Emerson has offered to volunteer her services to MAPS, and thus would be considered biased by the IRB, she nevertheless adds a level of expertise in FDA compliance and data monitoring that will help ensure that the study is conducted according to proper procedures. Ms. Emerson is available to meet with the IRB should a meeting be requested.

MAPS' FINANCES

A note about MAPS' finances is in order, since the panel's recommendation that MAPS turn the project over to a CRO was made in part because "MAPS has a significant level of funding." Actually, adding the costs of a CRO to the MDMA/PTSD study budget would be a difficult burden. MAPS has seen substantial reductions in donations over the last several years, with income for FY 2002-2003 expected to total about $450,000, less than half the amount MAPS received two years ago in FY 2000-2001, and $325,000 less than donations in FY 2001-2002. Most of MAPS' income is in the form of restricted donations for specific projects other than the MDMA/PTSD study, with these funds not available for use in the MDMA/PTSD project. Unfortunately, unrestricted donations do not cover basic operational costs, even with MAPS' relatively low salaries. As a result, MAPS has seen its reserves (created as a result of a roughly $450,000 bequest in 1996) decline over the last several years with this decline continuing despite staff layoffs and reductions in hours.

MAPS thus must fund the MDMA/PTSD project out of restricted donations specifically for this project, or through further drawing down our limited reserves. Over the last several years, MAPS has raised almost $195,000 in donations for Dr. Mithoefer's MDMA/PTSD study. Over $70,000 has already been spent on the lengthy protocol design and approval process (not including my time which is allocated to operational costs, not specific projects), leaving about $120,000 in hand. Over $100,000 from reserves has been spent on the MDMA literature review. The budget for the study is currently at $245,000, which includes the addition of $40,000 for the board-certified emergency physician and registered ER nurse and $15,000 per year to cover the costs of a $2 million insurance policy to indemnify the IRC in case of lawsuit. MAPS still must raise another $125,000 for this study, although at present I have no active grant applications or promising leads. MAPS' remaining reserves of about $170,000 can cover the costs of the study if no new funds are raised, but then MAPS is left with little to cover the shortfall between donations and operational costs.

SUMMARY REGARDING CSO ISSUE

Since the integrity of the data gathering process does not seem to us to be fundamentally improved by CSO monitoring as compared to the services to be provided by Dr. Mark Wagner and Amy Emerson, is not required by FDA for whom this study is primarily

being conducted, is not essentially a matter of patient safety, and would represent a substantial financial burden, we request that the IRB reconsider this recommendation.

SINGLE SITE V. MULTI-SITE PILOT STUDY

We understand and appreciate the goal of reducing bias that lay behind the suggestion that we add a second site to this study. However, doing so presents so many practical and theoretical problems that we request the IRB reconsider this request.

A multi-site study requires a standardized experimental intervention (note that I didn't say treatment) but at this time a standardized experimental intervention does not exist. One of the major purposes of this single-site pilot study is to gather preliminary evidence about both safety and efficacy in order to refine the experimental intervention. After we complete this initial pilot study, a subsequent single-site study will be required to standardize the intervention and operationalize a method and checklist for outside observers to evaluate whether the standardized intervention is being accurately delivered. Only after these two pilot studies have been completed would we be ready to move into a multi-site study design.

Data analysis with two sites is also significantly complicated as a result of the smaller number of patients at each site and potential interactions between the different experimental teams and patient safety and outcome measures.

It is doubtful that we or a CRO could find as qualified a second experimental team to conduct this initial pilot study as Dr. Michael and Annie Mithoefer, RN. I spent two years looking for a psychiatrist who had the proper qualifications to conduct this study before finding the Mithoefers. We are in essence inventing a new experimental intervention with the skills required to develop and refine new or experimental interventions being rarer than the skills needed to follow an already pilot tested and standardized experimental intervention. The years of special training that both Dr. Michael and Annie Mithoefer, RN have received from Dr. Stan Grof in the use of breath to induce altered states of consciousness that could then be put to therapeutic purposes was a very important part of the qualifications that I looked for in a PI and co-deliverer of the experimental intervention. Dr. Mithoefer's dual training as a psychiatrist and as an emergency room physician was another reason why I selected him as the PI for this study, with these skills highly valued by the FDA as well.

Neither Michael nor I know of another psychiatrist and associated co-deliverer of the experimental intervention who are interested in and sufficiently qualified to conduct this pioneering pilot study. I think that the IRB could justifiably be called to account for increasing the risk to patients if a second, less qualified experimental team were to be insisted upon before the uniquely qualified team of Dr. Michael and Annie Mithoefer, RN were given a chance to refine and standardize the treatment.

If we were required to find another experimental team, we would most likely end up selecting an academic research psychiatrist affiliated with an institution. This would

therefore require yet another IRB, which may or may not approve of the study. We'd also need to go back to the FDA for the revised protocol, which FDA might not approve since it is highly unusual to conduct a multi-site study without first conducting a single-site pilot study in order to develop a standardized intervention. I can easily imagine that trying to arrange for two sites would delay the study for at least a year, if not forever.

SUMMARY REGARDING SINGLE V. MULTI-SITE PILOT STUDY

The primary purpose motivating the panel to propose this protocol modification was to reduce bias in data gathering. Given the tremendous complications and delays that actually implementing a second site would involve, we request that the panel reconsider this proposal. We hope that the panel will be satisfied that we have done an adequate job of ensuring reliable data after it reviews the new information about Dr. Mark Wagner's professional expertise, procedures and the criteria by which he was selected, and about Ms Amy Emerson's professional expertise and her work on data monitoring and FDA compliance issues,

From our reading of the rest of your letter, all the other issues seem relatively easy to resolve. We will follow up with a revised and expanded version of this letter within a week or two.

Sincerely yours,

Rick Doblin, Ph.D.
MAPS President