

December 2, 2009

RE: Protocol#: MT-1

“A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers”

Dear _____

Here is our response to your deferral letter dated October 26, 2009. Questions or comments from the Board are italicized, and our responses are given below each question or comment.

1. The Board remains unconvinced regarding the scientific merit of this study. Further explanation and rationale as to why therapists need to undergo this in order to be effective in performing therapy is requested. Are there other psychoanalytic agents that therapists take as part of their training and work that parallel this situation?

First, we will address the scientific merit of the study protocol. Then we will address why it is important for us to be able to offer an MDMA-assisted psychotherapy session to therapists who are being trained to conduct MDMA-assisted psychotherapy research in the sponsor’s Phase 2 and potentially Phase 3 MDMA/PTSD studies.

1. Scientific Merit

Our proposed study is a randomized, double-blind, placebo-controlled crossover design, a design commonly used for examining drug effects, and used previously in the MDMA literature. Completed Phase 1 studies have assessed mood in laboratory settings using within-subjects crossover designs and doses similar though slightly lower than those we propose (Dumont and Verkes 2006). No studies in the scientific literature have assessed acute effects of full-dose MDMA administered in a therapeutic setting to healthy volunteers.

It has been repeatedly observed in the early literature of psychedelic therapy that “set and setting” have an important effect on a person’s experience following drug administration. The lack of any studies in normals in a setting similar to that used in clinical trials with psychiatrically-ill subjects represents a significant gap in the literature. Since Phase II and potential Phase III trials studying treatments of people with psychiatric illness occur in a therapeutic setting, and because it seems reasonable that setting may impact the experience of drug effects, it is of scientific merit to study the effects of MDMA in a therapeutic setting on healthy people without psychiatric diagnosis.

FDA reviewers expressed an interest in data on changes in mood state and psychological symptoms in this setting. Assessment at multiple intervals should allow for detection of changes associated with MDMA within a setting involving many of the procedures that

will occur during MDMA-assisted psychotherapy research, making the results relevant to understanding MDMA effects in a psychotherapy context. To date, this study will be the only examination of subjective drug effects in a psychotherapeutic setting.

A majority of the measures employed in this study are well established. The Profile of Mood States (POMS), has been used before in Phase 1 studies but that research was not conducted in a therapeutic context (Kuypers et al. 2008; Tancer and Johanson 2003). The use of this measure will enable us to compare the effects of context on the mood states produced during an experience of MDMA. The Brief Symptom Inventory (BSI) is a shortened version of the Symptom Check-list 90 (SCL-90) that we used in our Phase 2 MDMA/PTSD pilot study.

One of the new safety measures is now required by FDA for all studies of psychiatric products. This new measure is the Columbia Suicide Severity Rating Scale (C-SSRS), which has not yet been administered to subjects receiving MDMA. Since this measure will be used in all future clinical trials of MDMA-assisted psychotherapy for PTSD, it will be valuable to have data using it with normal volunteers receiving MDMA.

The study will also assess potential signs of changes in personality occurring after MDMA administration. This will allow comparison with the results in people with PTSD using the same personality measure, the NEO (Neuroticism, Extroversion, Openness Inventory), that we used in our recently completed Phase II trial treating people with PTSD.

This protocol is the first study to investigate the effects of MDMA on self-reported feelings of interpersonal closeness. We are using a new measure that has been designed by Lisa Jerome, Ph.D. This measure will be used in this protocol for the first time and has not been validated, but may be developed further for use in later studies. This is an exploratory study and the use of a new measure is appropriate. This measure could potentially develop into a valuable instrument to further understanding of one of the apparent effects of MDMA. Our conclusion based on extensive literature review and discussion with experts in the field is that there is currently not an adequate measure for this purpose that is suitable for use in clinical MDMA trials.

2. Selection of Sample and Training Component

To clarify, we believe that therapists can be effective in administering MDMA-assisted psychotherapy if they have not experienced MDMA-assisted psychotherapy themselves. We explicitly do not require the therapists working on our MDMA/PTSD studies to have a personal experience with MDMA; it will be offered only to those who volunteer. Rather, we believe that therapists who volunteer to have a personal MDMA-assisted psychotherapy session may potentially gain the benefit of being more effective in administering MDMA-assisted psychotherapy as a result of their understanding of the subjective nature of the MDMA experience.

There are potential safety advantages for the subjects in our future studies if their therapists have had a personal experience with MDMA. Receiving MDMA under the direction of investigators will provide therapist trainees with an in-depth understanding of the therapeutic effects of MDMA as well as the side effects. It will allow therapist trainees to better draw distinctions between common, self-limited side-effects of MDMA-assisted psychotherapy and those effects that require intervention. It will also help therapist trainees better understand how their subjects can process emotionally painful material. This may enable them to learn more about when it is appropriate to invite subjects to look deeper at an issue or to let them move their attention elsewhere.

Advantages of our Subject Population for this Phase 1 Protocol

The population of therapist trainees is limited to medical doctors, licensed psychologists, nurses, social workers, and students in graduate programs leading to degrees in psychotherapy. Due to their professional training and experience, these are all people who can be expected to have an above-average ability to evaluate the scientific literature concerning the risks of MDMA and to understand the content in the Informed Consent Form. This population is advantageous for ensuring fully informed consent.

The physicians, licensed psychologists, nurses, social workers, and students in graduate programs leading to degrees in psychotherapy who will volunteer to be the subjects in this study are also people we assume may benefit to some degree from their participation. One function of this study is to gather information to use to evaluate this assumption.

We believe that there is a favorable risk/benefit ratio for the study as described in the protocol, including offering it to health care professionals as an optional part of the training program. The FDA issued a "May Proceed" letter for this study including the selection of this sample.

MAPS participated in two teleconferences to discuss this protocol with the FDA's Division of Psychiatry Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research. Each call included Division Director, Thomas Laughren, M.D. During these calls, we came to agreement on a design of a study with dual purposes, both legitimate in their own right and mutually reinforcing.

One purpose of this protocol is as a Phase 1 exploratory study to gather useful scientific information about the psychological effects of MDMA in healthy volunteers receiving MDMA in a therapeutic context, within a randomized, placebo-controlled, double-blind crossover study.

A second purpose is to provide legal opportunities for so-inclined therapists in our training program to gain valuable professional experience that we believe may help us improve participant outcomes in terms of both safety and efficacy.

In the long run, should MDMA ever become a prescription medicine, FDA is likely to require physicians to complete certain training programs before they can prescribe

MDMA. How these training programs should be structured, and whether they may include the opportunity to volunteer for an MDMA-assisted psychotherapy session, are questions that we beginning to address in this protocol and in our therapist training program.

At present, there are no parallels to this situation because there are no psychoanalytic agents that therapists administer acutely to patients to enhance the psychotherapeutic process. However, personal therapy and the experiencing of one or more elements of psychotherapy while in training to become a psychotherapist has been and continues to be a common practice in training to be a psychotherapist. For example, psychiatrists who seek to become psychoanalysts must first go through their own psychoanalysis. Practitioners of Eye Movement Desensitization and Reprocessing (EMDR) for the treatment of PTSD undergo EMDR themselves during their training. It is because MDMA is a controlled substance that our training program needs to involve an FDA-cleared and IRB-approved protocol in order to provide an analogous experience for our trainees.

All four of the therapists conducting MAPS' Phase 2 MDMA/PTSD pilot studies who have had prior personal experience with MDMA in a therapeutic setting before MDMA was criminalized (Dr. Michael Mithoefer, Annie Mithoefer, BSN, Swiss psychiatrist Dr. Peter Oehen, Swiss psychologist Verena Widmer), believe their subjective experience with MDMA has helped them to become more effective in administering MDMA-assisted psychotherapy to their subjects. The two co-therapists who will soon start our Canadian MDMA/PTSD (approved by Health Canada and IRB Services), Canadian psychiatrist Dr. Ingrid Pacey and Canadian psychologist Andrew Feldmar, MA) have also had prior experience with MDMA in a therapeutic setting before MDMA was criminalized. They believe they will be more effective in administering MDMA to subjects as a result of their prior experience with MDMA in a therapeutic context.

Virtually all the pioneering psychiatrists and psychologists who conducted LSD research are of the opinion that self-experience with LSD enhanced their ability to administer LSD within a clinical context.

There is a precedent in the history of the Food and Drug Administration (FDA) for the administration of MDMA in the context of a training program. In the 1970s, in the "Training Project for Mental Health Professionals" conducted at the Maryland Psychiatric Research Center under Dr. Albert Kurland's IND for d-lysergic acid diethylamide (LSD), 108 people with pastoral and counseling jobs were permitted by the FDA to receive LSD up to three times in a therapeutic context. The purpose of the program was to help the mental health professionals to better understand the LSD experience so as to enhance their ability to work with people who discussed LSD experiences with them.

William Richards, Ph.D., a therapist who administered the LSD to many of these mental health professionals, has written a description of the program for our submission of this protocol to the FDA. He reports in his letter, included in this submission, that "in those

days, all clinical employees at the Maryland Psychiatric Research Center (psychiatrists, psychologists, psychiatric nurses) involved in interactions with human subjects during the period of psychedelic effects participated in a similar training program as part of their on-the-job training when they first were hired.” Daniel Helminiak, a therapist who participated in this program, believed that he benefited as a therapist from undergoing experience with LSD, as he expressed in a letter submitted to the FDA in support of this protocol and included along with this response.

Currently Richards is working as a therapist on research at Johns Hopkins being conducted by Principal Investigator (PI) Roland Griffiths, Ph.D., investigating whether psilocybin can generate mystical experiences (Griffiths et al. 2008; Griffiths et al. 2006). Richards is also a therapist on a second study at Johns Hopkins examining the role of psilocybin-assisted psychotherapy in treating cancer patients with anxiety. He is the most experienced psychedelic psychotherapist and researcher still working in the field, and his views on the value of subjective experience in the training of the therapist carry considerable weight.

In association with lead author, Matthew Johnson Ph.D., William Richards and Roland Griffiths have recently published an article in the Journal of Psychopharmacology, entitled, “Human Hallucinogen Research: Guidelines for Safety” (Johnson et al. 2008) (attached along with this letter). They discuss the desired qualities and training of the research team members who they call “study monitors”, who are present with the patient during his or her psychedelic experience. MAPS calls these people “co-therapists.” They write, “Monitors should have significant human relation skills and be familiar with descriptions of altered states of consciousness induced by hallucinogens. Personal experience with techniques such as meditation, yoga, or breathing exercises may also prove to be helpful in facilitating empathy for volunteers that experience altered states of consciousness during hallucinogen action.” (underline added). In their attached letter, prepared for submission to [the IRB] in support of this protocol, they go on to say,

Although not specifically stated in the above quote or elsewhere in our manuscript, we believe that, if conducted in a safe and legal clinical context as proposed in your protocol, administering the hallucinogenic compound (e.g., MDMA in your study) to the therapists/monitors as part of their training is likely an optimal approach for helping therapists/monitors understand the subjective effects of the compound and therefore to facilitate empathy for volunteer/patient experiences.

2. The Board sees no justification for allowing any subjects who may require discontinuation of any required medications. The Board also regards the population of those who “have successfully completed a sponsor-supported program for training therapists to perform MDMA-assisted psychotherapy research” as distinct from the title’s use of “healthy volunteers.”

In this study, we exclude people with current psychiatric disorders from participating in the study. However, some psychiatric medications are in use for other conditions, such as bupropion for smoking cessation or fluoxetine for premenstrual symptoms, and we wish to still enroll people who may take these medications and who can stop taking them with approval of their own doctor.

As we have explained in response to Question #1, MAPS and FDA have worked together to develop a protocol that meets both goals of being a scientifically meritorious Phase 1 investigation of the psychological effects of MDMA in healthy volunteers in a therapeutic setting and of creating an opportunity for therapist trainees to volunteer for the study for training purposes. Therefore, we are enrolling subjects who meet both criteria, who are “healthy volunteers” who “have successfully completed a sponsor-supported program for training therapists to perform MDMA-assisted psychotherapy research.”

3. Please justify why there are no pre-post cognitive function assessments.

In our recently completed Phase 2 US MDMA/PTSD pilot study, we conducted pre-post cognitive function assessments after two MDMA-assisted psychotherapy sessions. There was no evidence of any changes in cognitive function (see attached section of Preliminary Data Report to FDA sent along with the initial protocol on June 19, 2009). Furthermore, a comprehensive literature review of MDMA and/or Ecstasy and cognitive function suggests no reason for concern from one exposure in a therapeutic context to 125 mg of pure MDMA followed after about two hours by the administration of an additional 62.5 mg.

MAPS will be gathering further neurocognitive data in a planned MDMA/PTSD pilot study to take place in Vancouver, BC. This study will be administering three MDMA-assisted psychotherapy sessions and will use two of the three tests used in MAPS-1-03-071 (PASAT and RBANS). If this study confirms the negative findings in our US MDMA/PTSD study, we will propose to FDA that no further neurocognitive testing be conducted in any of our subsequent studies.

The study under consideration involves only one MDMA administration. Based on the existing data, we do not think the expense or the time required of the subjects to do neurocognitive testing is warranted.

4. What is the estimated number of potential participants who have successfully completed the sponsor-supported program for training therapists to perform MDMA-assisted psychotherapy research? Explain how these potential participants are recruited and how any potential undue influence will be addressed.

At this point in time, there are six potential participants eligible for the protocol who have successfully completed the sponsor-supported program for training therapists to perform MDMA-assisted psychotherapy research. All six took part in a week-long training program that MAPS held in Austria in June, 2009. Of these, two are already conducting a MAPS-sponsored MDMA/PTSD pilot study (in Israel) and one of the two has expressed interest in participating in this protocol. Additional training programs will be scheduled as the need arises. We expect to schedule another training program in early 2010 for the four Jordanian co-therapists who will be conducting a study of MDMA-assisted psychotherapy in people with PTSD in Jordan. If any of these co-therapists are interested

in participating in this protocol, they would do so after the training program. It appears that up to five of the therapists currently working on or preparing to work on MAPS Phase 2 protocols would be eligible and interested. The rest would come from therapists who complete the training to work as therapists in MAPS' additional Phase 2 and potential Phase 3 trials in the future.

Participants in our training program are recruited either after the therapists contact MAPS to inquire about conducting MDMA/PTSD research or after MAPS seeks out therapists in specific countries or locations in the US in accordance with MAPS' plans for Phase 2 studies.

Undue influence is avoided because, as already stated in the protocol, it is MAPS policy that the sponsor does not and will not insist on personal experience with MDMA prior to hiring therapists to conduct our MDMA research. For example, the investigators conducting MDMA-assisted psychotherapy research in Israel have no prior experience with MDMA.

Undue influence is further avoided because the people who can qualify for the protocol are highly educated in either medicine or psychology and can be expected to be among the group of people most able to evaluate the risks and benefits presented in the informed consent form. We will not attempt to recruit anyone for this study outside of this group of individuals. Both through undergoing the training and reading the consent, participants will be aware of criteria they will have to meet for it to be safe and appropriate for them to participate if they should choose to do so.

5. Please confirm validation of the psychological instruments utilized, particularly the novel interpersonal closeness measure. The references are noted. Are there references (or actual literature) related to the development and validation of the interpersonal closeness measure that could be provided, particularly as it is a primary objective?

Information on measures can be found both in 2.3 and 6.1.1 of the study protocol. The POMS is a well-established measure of current mood state. As indicated in the protocol, it has already been used in Phase 1 studies of MDMA, though not in a therapeutic context. The BSI is similar to the SCL90-R, the measure employed in Dr. Mithoefer's initial study (MAPS-1-03-077), and is a recognized measure of psychological symptoms. The NEO has also been used in our US MDMA/PTSD study. These measures and the C-SSRS, a clinician-administered assessment of suicidality, were all suggested to us by FDA reviewers, and the C-SSRS is a required measure for psychiatric products reviewed by FDA. We can if requested provide publisher information on the POMS and BSI.

There are no references for the interpersonal closeness scale; it was developed in response to the study requirements after the sponsor research specialist investigated other options for assessing this potentially therapeutic effect of MDMA. The interpersonal closeness scale uses visual analog scales (VAS) for responses, a scale format frequently used in Phase 1 studies of MDMA. The measure was created in part because there are no appropriate self-report measures of state interpersonal closeness. Because this is a new

measure assessing self-perceived interpersonal closeness in this setting, we have now concluded that assessing this potentially therapeutic effect is a worthwhile secondary objective, but not a primary objective. The Objectives Section in Amendment 2 has been updated accordingly. We will explore the possibility of including this measure in future sponsor-supported studies based on the pilot data from this study.

6. Confirm the capability of measuring changes pre- and post-MDMA use and the relationship of these measures to PTSD treatment, as the protocol purpose states: "...it may permit comparison between personality assessment in people with PTSD and healthy volunteers before and after MDMA administration." Are the same measures used in those studies of PTSD that are intended to be compared?

As described above and within the protocol, only one measure, the NEO, addresses personality changes over time, while the BSI assesses changes in psychological symptoms and the C-SSRS assesses suicide risk. The POMS is a measure of acute effects.

The NEO was employed in Dr. Mithoefer's completed Phase II investigation, and therefore data can be directly compared between the two studies. While the NEO was repeated after two MDMA-assisted psychotherapy sessions in the Phase II trial of MDMA-assisted psychotherapy rather than after one session in this study, it will be administered at the same time point, two months after MDMA administration.

The hypothesized therapeutic effects of MDMA may depend in part on changes in current mood state and interpersonal closeness. Increased positive mood without reduced awareness of other emotional states and increased trust and affiliation with therapists and other individuals may both serve to create a safe setting in which to confront emotionally intense or upsetting material. While previous research has investigated the acute effects of MDMA on current mood state, these studies occurred in laboratory settings and did not employ the structure used in MDMA-assisted psychotherapy (such as presence of male and female co-therapists, use of introspection or music). Assessing changes in mood and interpersonal closeness in healthy volunteers in this setting may provide new insight into how these processes work in people with PTSD.

7. Please provide a copy of the fourth reference: Ruse, J.M., et al., MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder: A Revised Teaching Manual Draft. 2008, MAPS.

Please find the latest revision of the manual included along with this submission.

8. Is the FDA aware of the source of the MDMA, as regards age of product? The purity testing information is appreciated. Has the product been used in the last three (almost 4) years, to provide indication of its continued clinical effect?

The FDA is aware of the source and age of the MDMA. As indicated in the report by David Nichols provided to the Board prior to review, it was used in another study not

supported by the sponsor during 2006. Three participants in MAPS' MDMA/PTSD study received MDMA in 2008, with full knowledge of the FDA.

Attached as part of this letter is the amended protocol that addresses the concerns of the board, and a consent form revised in accordance with the comments provided by the board.

This protocol is a key part of our overall drug development plans. We look forward to hearing from you regarding our responses to your initial questions.

Sincerely,

Rick Doblin PhD

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- Griffiths R, Richards W, Johnson M, McCann U, Jesse R (2008) Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol* 22: 621-32
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- Johnson M, Richards W, Griffiths R (2008) Human hallucinogen research: guidelines for safety. *J Psychopharmacol* 22: 603-20
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Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Protocol: MT-1

Title: A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers

Principal Investigator: Michael C. Mithoefer, M.D.

Re: Response to questions from the October 21-22, 2009 review

The following questions were submitted to principal investigator Michael Mithoefer MD, and MAPS on October 21-22 in response to a protocol submitted for review on October 15, 2009 and reviewed on October 22, 2009. Answers were initially compiled and supplied by MAPS via email. The answers below have been further revised.

1. Are there plans for an updated Investigator's Brochure? There is no section on actual drug physicochemical properties and clinical formulation, such as manufacturing, stability, current source of drug for studies.

The current investigator's brochure was completed December 2007. We have plans to update the Investigator's Brochure no later than June 2010. We have sent several reports reviewing relevant studies to the board in 2008 and most recently for 2009. Some of the requested information is contained within Section 4 of the study protocol. Information on physical properties may be added to the next update of the IB. Specific information on manufacture is not usually part of an investigator's brochure, as material may come from different sources. FDA has periodically requested re-analysis of the material to be used in this study, with the last analysis occurring in February, 2006, as noted in response to #5, below.

2. Please advise on the current status on the PTSD Israel study.

This study is ongoing. Four participants have completed the treatment phase of the study, with one completing all the study follow-up evaluations. There have been no drug-related serious adverse events reported by the site. The study will be complete when 12 participants have enrolled in the study and have completed 12-month follow-up.

3. Protocol Section 5.3.2 Exclusion criteria starts with # 15. Is this numbered incorrectly, or are there 1-14 criteria missing?

This is an error in the document; as previously communicated and now clarified further; there are fifteen inclusions, that should be numbered 1 through 15, and 12 exclusions that should be labeled 1 through 12. This has been corrected in Amendment 2 of the protocol.

4. Is there a need to exclude lactose intolerant subjects, or include risks of lactose intolerance in Informed Consent, given its role as placebo?

Capsules will contain an equivalent weight of 125 and 62.5 mg lactose. The amount of lactose used in placebo capsules is not large enough to be of concern for lactose intolerance. The same amounts were used in the initial study of MDMA-assisted psychotherapy, M-P1 (MAPS 1-03-077) without any problems. A statement concerning the amount of lactose to be used in the study is in the revised consent materials.

5. Please confirm the GMP of the compounding pharmacy. Does this pharmacist meet his applicable//comparable DEA requirements for handling this Schedule 1 drug? Was this pharmacy used in the U.S. PTSD study?

In Section 4.3 of the protocol, the text states: "Compounding will be done by a pharmacist under the direct observation of the investigator who has been issued the Schedule 1 license. In order to maintain the blind, a randomization monitor (described below in section 5.2) will supervise placement of the capsules into groups of four smaller containers and these will be placed into larger containers numbered in accordance with a randomization list (four smaller containers per large container, and one large container for each potential subject, with extras for possible dropouts)."

The study PI is the DEA license holder for the Schedule 1 compound. According to DEA regulations, the pharmacist does not need to have a similar license so long as the license holder is in the presence of and observing the compounding. This is the same general procedure as for study MP1 (MAPS 1-03-077) which Dr. Mithoefer arrived at after discussion with the DEA, except that this study is a crossover study and the previous one used a between-group comparison.

6. Protocol Section 4.6 discusses MDMA Stability. This section discusses "purity" of substance, but does that equate with drug "stability," particularly if this batch is from 1985? Is the actual source of MDMA for this study from the 1985 Purdue batch? How is the effectiveness of this assured? What have been the storage conditions of this for the last 20+ years? If this is not the source, please provide all details of MDMA source, including but not limited to GMP conditions. The protocol in Section 4.3 states passively "MDMA in bulk will be sent to the investigator..." Sent by whom?--Provide more detailed drug handling.

The MDMA to be used in this study is from the same 1985 Purdue batch of MDMA that was used for the first MAPS study. It was used as recently as 2006 for a study conducted by Dr. Carl Hart of Columbia University, and three participants received this MDMA in 2008 during the course of MP1 (MAPS-1-03-071). We have submitted a document describing both the conditions under which the MDMA is stored and an analysis conducted by Dr. Nichols in February, 2006 in response to a request related to the Dr. Hart's study. Upon arrival to the study site, it is stored in a locked safe in accordance with regulations. The material is sent by Dr. Nichols or his representatives at Purdue University to Dr. Mithoefer, who holds the Schedule 1 license, and he takes the bulk product to a pharmacist for compounding in his presence, also as required by federal regulations. Information on who has sent the product is provided in the amended protocol. The compounding is described in the protocol. The investigational compound

will be stored at room temperature in a safe, under the same storage conditions as for study MP-1 (MAPS-1-03-071).

7. Explain how the PI will dually serve as medical monitor and as PI for the study, and how the Sponsor designee as PhD will be medically qualified and objective, also given their conflict of interest.

Addressing concerns about the dual role for medical monitor that will arise in this study, MAPS has located another medical monitor, Dr. Julie Holland, who has agreed to serve in this role. She has been added to Amendment 2 as the medical monitor.

8. Please provide a more detailed list of actual allowed and disallowed concomitant and rescue medications, for example as a protocol appendix. This would include washout times for those disallowed psychotropic medications.

Medication washout will be five times the medication half-life, regardless of medication identity. This qualification is present within the list of inclusion factors, but will now be stated in the relevant text on screening and included in amendment 2. Excluded concomitant medications include antidepressant, antipsychotic or sympathomimetic medications, or anything causing monoamine oxidase inhibition. Rescue medications include benzodiazepines or zolpidem.

9. Provide a copy of the CRF.

Please find attached along with this memorandum a copy of the CRFs.

10. Protocol Section 5.0 Study design states subjects will have their integrative session on the day after the first experimental session. Then, “On the following day they will undergo a second day-long experimental session,…” Confirm this “following day” is the day after the integrative session, such that subjects have a night away from research site.

The second experimental session occurs on the day after the integrative session. This will give them a night away from the research site. This information is also present on the table in the protocol right before section 6.2 (Visit Descriptions) and it titled Time and Events table. Readers will note that Visit 2 and 4 are experimental sessions and Visit 3 and 5 are Integrative Therapy sessions.

11. Given that subjects may come from other parts of the country, and given that the Informed Consents states that “You will need to arrange ahead of time to have someone take you home from this non-drug session because we do not know how or for how long MDMA will affect your ability to drive.” Please explain more fully whether “home” is a hotel room, before and between and after sessions. Also, how long after study completion do subjects need to stay in the local area?

Home can refer to current location where person is staying (as a hotel). The consent document has been revised accordingly.

12. Provide qualifications of the “therapeutic assistant or therapist” listed in Appendix A Option A. to stay with an agitated or psychologically unstable subject.

The attendant will not be required to stay with an agitated or psychologically unstable subject. Since these subjects are normal controls without psychiatric diagnosis and since the investigators will not leave until they are psychologically and medically stable, and since the investigators are only 10 minutes away and will be on call to return if necessary, neither the sponsor nor the investigators think the attendant needs to be a nurse (as he or she was in the initial study, MP-1) It will be an individual whom the investigators have selected to be reliable and sensitive and who is trained to be supportive but not intrusive and to call the investigators in the case of any questions or concerns. It may be someone whom the subject has requested if the investigators have met with them, judge them to be suitable and given them instructions.

13. Does the local hospital to which Option B applies require pre-notification to assure bed availability? Is this hospitalization cost the subject’s responsibility? Please include this information in the Informed Consent.

The local hospital to which Option B applies does not require pre-notification. The hospital has a 24 hour ER to accept patients and has the capability to keep someone in that area if they need admission and there is no inpatient bed. Any medical expenses not covered by the person's insurance, including hospitalization, will be paid by MAPS if the problem is caused by study participation. A general statement already exists to this effect under “Treatment and Compensation for Injury.”

14. Costs noted in Informed Consent discuss ‘travel expenses to and from the research location’. Does this include lodging costs? Please apprise subjects of this in the Informed Consent. Justify cost coverage based on conduct of a MAPS-sponsored study or not.

Subjects will not be paid for travel or lodging costs for MT-1 (as opposed to MP-1). This is now stated in the revised consent.