October 10, 2002

James R. Baldwin, PhD
Executive Director
WIRB
3535 Seventh Ave. SW
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Multidisciplinary Association for Psychedelic Studies Protocol #63-384
WIRB #20021019/1040339

Dear Dr. Baldwin,

Thank you very much for having had such a reasonable and kind discussion over the telephone with me on October 3, 2002. I greatly appreciate it. I am writing now to request the opportunity to address the Board in person concerning the Multidisciplinary Association for Psychedelic Studies' FDA-approved Protocol #63-384, investigating MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD). If his schedule permits, Dr. Mithoefer, the Principal Investigator (PI), would also like to attend. Dr. Mithoefer is currently on vacation, so I will get back to you as soon as I hear from him about which Wednesday, if any, we can both come to meet with the IRB panel. As we discussed, we have tentatively set the date for October 30.

I'm sending this written submission now, in order to give the panel ample time to review our documents and contact any additional outside experts that the panel thinks appropriate. In addition to this letter, we are also submitting for your review letters of information and/or support for the protocol from thirteen experts whose first-hand written submissions should help the WIRB panel evaluate various issues raised in Mr. Jacobs' letter. Some of these letters were originally written for submission to FDA while others were specifically written for submission to the WIRB.

In support of the WIRB reconsidering our protocol, please refer to the letter submitted by the following researcher:

1) Dr. Reese Jones MD, Professor of Psychiatry, Langley Porter Psychiatric Institute, University of California San Francisco. Ex-Chair of the UCSF Medical Center IRB. Letter dated October 9, 2002.

In Mr. Jacobs's letter of September 6, he informed us that the Western Institutional Review Board's (WIRB) July 10, 2002 approval of our protocol was being withdrawn because the research "presents unacceptable risks to subjects." We were dismayed that the decision to revoke approval was based on second-hand reports of conversations that a representative of the WIRB had with three researchers, with no written position statements from the researchers themselves. Most importantly, the revocation was not based on specific data. We were surprised that we were not given a chance to respond to the concerns expressed by these researchers before action was taken to withdraw

approval, and hurt that Mr. Jacobs felt it necessary to criticize us personally for presenting information that "omits significant facts" and for appearing to "lack the scientific objectivity and rigor required to carry out this research." The Board appears to confuse risks associated with ongoing abuse of MDMA in uncontrolled settings with the much lower risks of the two modest oral MDMA exposures proposed in our protocol.

Since we believe your withdrawal of approval was based on a series of misunderstandings, my chief goal in writing you is to act as a problem-solver. We believe we can work together to resolve these misunderstandings so that we can come to an agreement to permit the study to go forward.

As Mr. Jacobs pointed out, the WIRB has a legal obligation to ensure that "the risks to subjects are reasonable in relation to anticipated benefits." See 21 CFR 56.111 (a) (2). This regulation clearly imposes on the WIRB the legal requirement to conduct a rational balancing of risks as well as benefits, based on data and not merely on personal opinion.

Mr. Jacobs raised five separate issues that I will address in the same order as in his letter.

I. The Board contends that "the investigator's brochure (IB) was compiled by three authors about whom there is insufficient or no information to assess their professional expertise and qualifications regarding the research."

Investigator's Brochures are not typically documents with authorship indicated. However, because of MAPS' commitment to full disclosure, biographical information about all three authors of the IB was included on Page 2 of the IB. We have supplemented this information in Appendix A. If any additional information is desired, we would be glad to provide it.

Most importantly, the Board claimed that the Investigators Brochure "minimizes the known toxicity of MDMA reported by other sources." It is true that after a rigorous and comprehensive review of the peer-reviewed scientific literature on MDMA, we concluded, and the FDA agreed, that the risks to subjects in our study were acceptable. However, a crucial distinction needs to be made. Concluding that there is a minimal risk of significant deleterious functional consequences to subjects resulting from the known toxicity of MDMA administered at the doses proposed in the protocol is not equivalent to "minimizing the known toxicity of MDMA reported by other sources."

In support of risk estimates in the IB and the associated protocol for direct neurotoxicity, please refer to letters submitted by the following researchers:

2) Jim O'Callaghan, Ph.D., Head, Molecular Neurotoxicology Laboratory, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. NOTE: Dr. O'Callaghan is expressing his own personal views. His letter, which is enclosed, should not be considered an endorsement by the Center for Disease Control and Prevention.

3) Stephen J. Kish, Ph.D. Head, Human Neurochemical Pathology Laboratory,Centre for Addiction and Mental Health, Toronto, Ontario. NOTE: Dr. Kish mailed his letter directly to James Baldwin, Ph.D.

4) Franz Vollenweider, MD, research scientist and lecturer at the University Hospital of Zurich, University of Zurich. He currently holds the title of Privat Docent, which is approximately equivalent to Associate Professor, in the School of Medicine.

5) David Nichols, Ph.D. Professor of Medicinal Chemistry and Molecular Pharmacology, Purdue University.

In support of risk estimates in the IB and the associated protocol that relate to the functional consequences of MDMA on cognitive function and memory, please refer to letters submitted by the following researchers:

6) Euphrosyne Gouzoulis-Mayfrank, MD, Psychiatric Dept. of the Rheinisch-Westflische Technische Hochschule, Aachen, Germany.

7) John Halpern, MD. Instructor in Psychiatry, Harvard Medical School, Alcohol and Drug Abuse Research Center, McLean Hospital.

In support of overall risk estimates in the IB and the associated protocol, please refer to letters submitted by the Principal Investigators of all three FDA-approved MDMA Phase I safety studies, from the following researchers:

8) Manuel Tancer, MD. Associate Professor and Associate Chairman, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine.

9) Reese Jones, MD, Professor of Psychiatry, Langley Porter Psychiatric Institute, University of California San Francisco. Ex-Chair of the UCSF Medical Center IRB. Letter dated July 25, 2001.

10) Charles Grob, MD, Professor of Psychiatry, UCLA School of Medicine

In support of overall risk estimates in the IB and the associated protocol, please refer to the letter submitted by the author of a recent, comprehensive book about MDMA:

11) Julie Holland, MD, Assistant Professor of Psychiatry, New York University School of Medicine. Author of Ecstasy: The Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA.

II. The Board stated that the IB "inappropriately references the study as coming out of the Medical University of South Carolina…the study is therefore subject to MUSC IRB oversight…"

The IB says nothing about where the proposed study will take place. Section 4 of the Board's own letter notes that the "MDMA research was to be conducted out of a private office as submitted for this study."

After further investigation, we think there is a chance that we may have identified where the Board got the impression that we were claiming the study was coming out of the MUSC. We were surprised to find that we had made a typographical error in the protocol posted on the MAPS website, in the Institutional Review Board section. However, we did not make this mistake in the protocol we sent you. In the protocol posted on the MAPS website, the first line says that we will be submitting the protocol to the Medical University of South Carolina IRB. The next line gives the address of the WIRB. It's clear we made a mistake in this section since the address for the MUSC IRB is obviously not the WIRB address. If anyone from the WIRB encountered this text, we apologize for inadvertently creating confusion by failing to correct the first line from a prior draft, written when we were considering applying to the MUSC IRB.

The appropriate IRB to review protocol is the WIRB. The protocol does not need to be submitted to the MUSC IRB

Mark Wagner, Ph.D, is a consultant on this study. The Chairwoman of the MUSC IRB and the Chairman of the Department of Neurology, where Dr. Wagner is Neuropsychology Division Chief, have informed him that he can consult on this study even if it is reviewed by an IRB outside of the MUSC.

Michael Mithoefer MD, the Principal Investigator of this study, is Clinical Assistant Professor of Psychiatry at the Medical University of South Carolina. Several months ago, when we submitted our protocol for review to the WIRB, Dr. Mithoefer submitted a letter to the MUSC IRB offering to resign his clinical appointment if the MUSC IRB determined that he could not serve as a PI on a protocol that was not reviewed by the MUSC IRB. At present, Dr. Mithoefer has not been asked to resign his clinical appointment.

III. The Board claimed that Bryan Roth MD PhD, project director of the National Institute of Mental Health's Psychoactive Drug Screening Program, was "opposed to any further human studies using MDMA." The Board claimed that "in addition to known neurotoxic effects, research on MDMA by Dr. Roth and others is discovering evidence of adverse cardiac valve effects."

A Medline search reveals that Dr. Roth has only one published, peer-reviewed paper involving MDMA. This study examines the affinity of the isomers of MDA and MDMA for the 5-HT2A and 5-HT2C receptors. This paper, on which David Nichols PhD is a co-author, is neither a study of neurotoxicity nor a study of MDMA's effects on cardiac valves. In order to better understand Dr. Roth's concerns, I contacted him directly. Dr. Roth explained that he had based his concerns about MDMA and cardiac valve effects on unpublished research that he and his associates have conducted in isolated human cardiac

valve cells.

After a series of conversations, Dr. Roth indicated that the statements attributed to him by the Board do not represent his current views. He supports the approval of our protocol with two conditions, 1) the informed consent form be modified to include text about possible cardiac valve effects and 2) two echocardiograms be administered to all the subjects, one before the first experimental session and one after the second experimental session.

Dr. Roth has provided us with language that he considered appropriate for addition to the informed consent form, which I am submitting below to the WIRB for consideration:

'It is known that fenfluramine (e.g. Fen/Phen; Redux) a drug similar to MDMA, causes heart valve problems (e.g. fenfluramine-induced valvulopathy) when given chronically and that MDMA and one of its metabolites (MDA) cause some of the same biochemical changes in isolated heart valve cells as fenfluramine. These findings suggest that MDMA and its metabolite MDA might cause heart valve problems if used in a way similar to fenfluramine.. At present, we do not know if MDMA causes the same heart valve problems as fenfluramine and, if it does, what the risk is to the individual user of MDMA. The risk of two doses of MDMA inducing heart valve problems is, thus, unknown but is probably very small.'

Regarding Dr. Roth's view that two echocardiograms be conducted, we are not convinced that echocardiograms are indicated in our protocol. We are, of course, willing to defer to the requirements of the FDA or the WIRB on this matter. Dr. Roth has sent me his unpublished data and I have submitted it to FDA for review as an addendum to our IND. If I hear anything from the FDA, I will immediately inform the WIRB.

There is only one paper in the MDMA peer-reviewed literature in which echocardiograms have been administered to human subjects. This study evaluated subjects who had used MDMA in recreational contexts for an average of 49 times. This study was conducted in the laboratory of Dr. John Mendelson at UC San Francisco (Matthew Baggott is a co-author on this paper). No evidence of preexisting heart valve changes were found in these subjects. The acute cardiovascular effects of MDMA were well-tolerated by the subjects, who were administered MDMA in a clinical setting.

We have written a more detailed analysis of the risk of MDMA causing significant heart valve problems to subjects in our study. This analysis can be found in Appendix B.

For an evaluation of the risks of cardiac valve effects to the subjects in our protocol, please refer to the following letter:

12) John Mendelson, MD, Associate Clinical Professor, Langley Porter Psychiatric Institute, Department of Psychiatry, University of California San Francisco.

IV. The Concerns of Una McCann, MD

The Board reported that Dr. McCann "revealed her reservations about subject safety if MDMA research was to be conducted out of a private office as submitted for this study."

We believe, as does the FDA, that our emergency response procedures are at least as good as what would be available in a hospital setting, and are arguably superior.

After reading Mr. Jacobs' letter, I called Dr. Una McCann and also George Ricaurte MD, Dr. McCann's husband and frequent research collaborator. I had several lengthy conversations with Dr. Ricaurte, but did not speak with Dr. McCann. Dr. Ricaurte acknowledged that neither he nor Dr. McCann are experts in emergency medicine.

While I certainly cannot speak for either Dr. McCann or Dr. Ricaurte, I was left with the impression, perhaps erroneous, that Dr. McCann was not fully aware of the exact combination of personnel and equipment that will be present in the private office setting, or that our emergency response procedures were negotiated and approved by the FDA's Division of Neuropharmacologic Drug Products, in consultation with FDA's Division of Cardio-Renal Drug Products.

Staffing includes a currently practicing, board certified, emergency physician and nurse in the next room for the first five hours of each MDMA session along with a fully-stocked crash cart in the treatment room itself. In addition, Dr. Mithoefer, who will be with each patient throughout the experimental session and will provide the therapy along with Annie Mithoefer BSN, practiced emergency medicine for over 10 years, taught emergency medicine at The Medical University of South Carolina, was director of two different county emergency rooms and medical director of two county EMS programs during those years.

Transfer by ambulance from Dr. Mithoefer's office to a nearby hospital would be only slightly longer than a trip through the halls and elevators of a university hospital. Most importantly, definitive emergency treatment would be delivered before transfer would be necessary with patients treated more rapidly in the private office setting than in a hospital.

Dr. Mithoefer sent a letter to Drs. Ricaurte and McCann describing in more detailed our emergency response procedures, This letter appears in Appendix C.

For an evaluation of the effect on patient safety of conducting the study in a private office setting with our specific combination of personnel and equipment, please refer to the following letter:

13) Howard Kornfeld, MD, Assistant Clinical Professor, Department of Medicine, University of California, San Francisco, Board-certified in Emergency Medicine, Co-Chair of the Resources and Development Committee of the American Society of Addiction Medicine.

The Board also reported that Dr. McCann said "that MDMA, as an amphetamine derivative, is the only psychedelic with neurotoxic effects". It's difficult to believe that Dr. McCann said this since she is well aware that MDA and other substituted amphetamines that have psychedelic properties are also neurotoxic, with MDA being roughly twice as neurotoxic as MDMA (Miller and O'Callaghan 1996; Molliver et al. 1990; O'Callaghan and Miller 1994; Ricaurte et al. 1985). The psychedelic drugs ibogaine and ketamine have also been shown to cause neurotoxicity at certain doses (O'Hearn and Molliver 1997; Olney 1989; 1991; Vocci et al. 1997). Furthermore, quite a few prescription medicines that are not psychedelic also cause some degree of neurotoxicity including fenfluramine, amphetamine, methamphetamine and a range of anti-psychotic medicines (Miller and O'Callaghan; Molliver et al. 1990; O'Callaghan and Miller 1994; Sabol et al. 1995; Seiden and Kleven 1989; Seiden and Sabol 1996).

The Board also reported that Dr. McCann stated that "there is no scientific evidence that MDMA has therapeutic effects- there are only unsubstantiated anecdotal reports." This is hardly an argument not to conduct a double-blind placebo-controlled pilot study. In fact, this comment highlights the need for such research. Many, if not most, medical discoveries originate in anecdotal clinical observation. Science advances when anecdotal evidence is tested in properly controlled studies that use well-defined populations and validated clinically relevant measurements. Furthermore, as Dr. Alan Leshner, ex-Director of NIDA, likes to say, the absence of evidence isn't evidence of absence.

In any case, there are also other kinds of evidence suggesting that MDMA's therapeutic potential deserves to be explored scientifically. Some of this evidence is from substantiated anecdotal reports (Adamson 1985); case reports written by psychiatrists; legal testimony before a DEA Administrative Law Judge about MDMA's therapeutic potential by psychiatrists who administered it to patients before it was illegal (online: http://www.maps.org/dea-mdma/); encouraging results from a retrospective questionnaire completed by more than 150 patients who were administered MDMA in Switzerland between 1988-1993 by a small group of Swiss psychiatrists who could legally treat patients with MDMA (Gasser 1994); and a published, peer-reviewed paper demonstrating therapeutic benefits in neurotic outpatients after administration of the related compound MDA (Yensen et al 1976).

Finally, Dr. Ricaurte and I discussed the possibility of having him and Dr. McCann review the informed consent form in order to assure that the risks are fairly presented. Unfortunately, we didn't reach any resolution on this issue. I cannot say whether Dr. Ricaurte or Dr. McCann would be willing to undertake this task. Nevertheless, I recommend that someone from the WIRB ask them directly to consider providing input into the informed consent form.

V. The Section about the MDMA itself, and David Nichols, PhD

The Board wrote that "information about this source of MDMA was not provided with the IB." That is true, since such information is not usually part of the IB. The

information that Dr. Nichols was the source of the MDMA to be used in this study was provided on page 11 of the protocol. A letter of support for this study by David Nichols PhD. is included in this mailing.

We definitely realize, as Mr. Jacobs pointed out, that a DEA Form 222 is required before Dr. Nichols can ship any MDMA to Dr. Mithoefer, and that Dr. Mithoefer must obtain a DEA Schedule I license before he can receive any MDMA. In fact, we indicated in the IRB application form that Dr. Mithoefer had already applied to the DEA for his Schedule I license, which he is still waiting to obtain.

We are well aware of the regulatory environment within which we must work. Perhaps it will reassure the Board to note that my dissertation topic for my Ph.D. in Public Policy was the regulation of the medical use of psychedelics and marijuana.
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I would like to briefly comment about several additional issues raised by Mr. Jacobs. He writes that the Board concluded that "MAPS appears to have presented information about MDMA for purposes of this research in a manner that omits significant facts…" This is a surprising comment, given that we submitted an IB that is the most comprehensive review of the peer-reviewed scientific literature on MDMA ever written. The only new facts that Mr. Jacobs identified in his letter are Dr. Bryan Roth's unpublished data, which we obviously can't be expected to have known about. Nor is it clear that these facts are significant in terms of risk. If there are other significant facts that we have omitted, we will eagerly work to take them into account and include them in our IB.

The Board was also concerned that Dr. Mithoefer and I "lack the scientific objectivity or rigor required to carry out this research." This claim seems based on our assessment that subjects in this study will be exposed to a minimal risk of functional consequences as a result of MDMA neurotoxicity. We hope that the letters we have submitted from experts in neurotoxicity research will enable the Board to see that we are not alone in our views, and that we are working as best we can to analyze the MDMA literature in an objective and balanced manner.

For a personal reference to Dr. Mithoefer's integrity and an expression of support for the protocol, please refer to the following letter:

14) Robert Malcolm, MD, Associate Dean for Continuing Medical Education, Professor of Psychiatry, Family Medicine and Pediatrics, Medical University of South Carolina.

We recognize the controversial nature of this project and are well aware of just how precious is the opportunity to conduct this pilot study. After struggling for 17 years to obtain permission for MDMA psychotherapy research, I will work to the utmost degree to ensure that we conduct ourselves as model researchers so as not to squander our first chance ever to conduct an FDA-approved, double-blind, placebo-controlled study examining the risks and benefits of MDMA-assisted psychotherapy. It is not possible at this time to say with confidence that we will actually be able to ease the suffering of any

PTSD patients. However, we do believe that it is possible at this time to say with confidence that the attempt is worthwhile, ethical, and that "the risks to subjects are reasonable in relation to anticipated benefits." See 21 CFR 56.111 (a) (2).

In conclusion, we'd like to reassure the Board that we will do everything in our power to ensure that this research study will be seen in retrospect as a credit to all concerned.

Sincerely yours,

Rick Doblin, Ph.D.
MAPS President

Appendix A
Qualifications of the Authors of the Investigator's Brochure (IB)

The primary author of the Investigator's Brochure (IB) is Matthew Baggott, who makes up in experience and knowledge what he lacks in an advanced degree. He began his career studying the neurotoxicity of amphetamines in the laboratory of Lewis Seiden Ph.D., in the Department of Pharmacological and Physiological Sciences, at the University of Chicago, from 1990 to 1993. During this period, Baggott and colleagues identified what may have been the first known behavioral consequences of methamphetamine neurotoxicity in drug-free animals (Baggott et al. 1992; Richards et al. 1993). In 1993, Baggott joined a group of researchers conducting clinical pharmacology experiments in the Department of Psychiatry at the University of California, San Francisco. With this group, Baggott investigated the effects of drugs of abuse and potential pharmacotherapies in healthy and drug-dependent individuals (e.g. Mendelson et al. 1996; Mendelson et al. 1999).

Baggott's publications on MDMA dating from his time at UCSF include a letter in the *New England Journal of Medicine* discussing a possible link between MDMA and Parkinsonism (Baggott et al. 1999), a research report in *JAMA* on the contents of illicit MDMA preparations (Baggott et al. 2000), a report in the *Annals of Internal Medicine* describing a clinical study of the acute cardiovascular effects of MDMA in healthy volunteers (Lester et al. 2000), and a report in *Psychopharmacology* describing a clinical study of the acute self-report and psychiatric effects of MDMA in healthy volunteers (Harris et al. 2002).

Baggott left UCSF in 2000 to concentrate on preparing the Investigator's Brochure for MAPS. Since leaving UCSF, Baggott has published a review in the *Journal of Psychoactive Drugs* discussing the consequences of illicit MDMA use and strategies for reducing use of MDMA by adolescents and young adults (Baggott 2002). In addition to journal publications, Baggott has written an invited chapter on emerging drugs of abuse (Bonson and Baggott 2002) for the *Handbook of Neurotoxicology Vol. 2* (ed., Massaro) and a chapter on MDMA neurotoxicity (Baggott and Mendelson 2001) for a book on MDMA edited by psychiatrist Julie Holland. In a recent review, this chapter on MDMA neurotoxicity was judged by the editor-in-chief of *Addiction* to be of "Pulitzer quality" with the authors described as "brilliant" (Edwards 2002).

As indicated on page 2 of the introduction to the IB, Baggott's co-authors on the Investigators Brochure are well-trained scientists. Ilsa Jerome, Ph.D. earned a doctorate in social psychology from the University of Maryland in 2001. Reid Stuart, MA, earned a master's degree in psychology with a specialty in addiction studies.

The Investigator's Brochure was informally reviewed for accuracy by a number of scientists and physicians, including specialists in the areas of pharmacology, psychiatry and neurotoxicity. The document has been posted on-line since August, 2001, and notices about the document were sent to all participants in the NIDA-sponsored conference on MDMA held in July 2001. The IB has been circulated to scientists within NIDA and

other NIH institutes and has been submitted to FDA. To date, feedback on the Investigator's Brochure has been uniformly positive.

Appendix B:
Risk of Adverse Cardiac Valve Problems from Clinical Administration of MDMA

Research by Roth and colleagues has identified an association between activity at 5HT2B receptors and valvular heart disease (VHD) (Rothman et al. 2000; Rothman and Baumann 2002). Because receptor binding profiles of MDMA were conducted before the identification of the 5HT2B receptor (Battaglia et al. 1989), no published data assessed the affinity for or activity of MDMA at this receptor. However, Roth and colleagues have found that MDMA and the MDMA metabolite MDA bind to the 5HT2B receptor in isolated human cardiac valve cells, and that both substances stimulate a mitogenic response in these cells similar to fenfluramine. These findings are suggestive of possible effects on valvular function from MDMA, but the doses of MDMA that produced these effects were higher than the doses of fenfluramine producing the same effects, and studies in humans indicate that MDA is a minor metabolite in humans (de la Torre et al. 2000; Fallon et al. 1999)

The putative risk for MDMA to produce cardiac valve effects was not addressed in the protocol or Investigators Brochure because no clinical or pre-clinical data had shown that this was a concern. A search of the PubMed medical database conducted on September 9, 2002 failed to find any case reports of valvular heart disease occurring after MDMA use. Perhaps the most relevant data come from Lester et al. (2000) who investigated the acute cardiovascular effects of MDMA in eight healthy MDMA-experienced volunteers in a NIDA-funded, three-session, double-blind, placebo-controlled study. These researchers used quantitative two-dimensional Doppler echocardiography to measure cardiac function before drug administration and during the approximate time of peak effects from 0.5 mg/kg (approximately 35 mg) and 1.5 mg/kg (approximately 105 mg) MDMA. Before participating in the study, the eight volunteers (and an additional individual who did not complete the study) were assessed for healthy cardiac functioning using intravenous infusions of dobutamine, a well-characterized beta-adrenergic agonist with peripheral sympathomimetic activity, and 2-D echocardiography. No abnormalities were seen in these volunteers, including one who reported having used MDMA over 200 times.

(See sbumitted attached letter from the senior investigator of this study, John Mendelson, a physician with extensive research publications on the cardiovascular effects of stimulants in humans.)

> The reported link between certain serotonin releasers used clinically as anorectics and valvular heart disease has been well-publicized. Nonetheless, these adverse events are sufficiently rare in patients taking anorectics that some large studies have failed to confirm that there is increased risk of valve problems in this population (e.g., no evidence of changes 4.9 years after 276 volunteers took 60 mg fenfluramine and 254 volunteers took placebo daily for up to three months in Davidoff et al. 2001). Estimates from these studies of the increase in incidence of valvular heart disease in patients taking fenfluramine have not, to our knowledge, exceeded 12% and several

studies have indicated the likelihood of disease increases with increasing dose and duration of drug use (reviewed in Rothman and Baumann 2002; Weissman 2001). Given that this disorder remains rare in individuals using fenfluramine or other serotonin releasers for months at a time, we think it is very unlikely to occur in our small study (in which MDMA is administered only twice). Thus, additional echocardiograms would be unlikely detect, confirm, or disapprove cardiac valve effects after MDMA.

Appendix C
Dr. Mithoefer's Letter to Drs. Ricaurte and McCann About Study Location

Michael C. Mithoefer, MD
208 Scott Street
Mt. Pleasant, SC 29464

Phone: 843-849-6899
Fax: 843-884-3010

September 14, 2002

Una McCann MD
George Ricaurte, MD

Dear Drs McCann and Ricaurte,

I'm writing to address the concerns I'm told you have about our proposing to do MDMA research in my office rather than in an inpatient setting. I share your desire to be sure all appropriate measures are taken to ensure subject safety in MDMA research. I am aware that there have been cases of sudden death in young, apparently previously healthy, individuals using Ecstasy in non-medical settings. It is not surprising that any drug with amphetamine-like effects would cause cardiac arrhythmias, including ventricular fibrillation, on rare occasions even in otherwise healthy people. We take this possibility very seriously and will be prepared to respond to any such complication. I will describe below our approach to this:

1) All potential subjects will be screened with a careful medical history, physical exam and EKG. This will eliminate anyone with a history of heart disease or cardiac rhythm problems, or anyone who has an abnormal rhythm, prolonged QT interval or other significant abnormalities on EKG. This should decrease the likelihood of complications from MDMA, but, of course, is no guarantee that a subject will not experience cardiac arrest.

2) We will have the equipment on hand to perform immediate defibrillation and cardiopulmonary resuscitation. There will be a "crash cart" with defibrillator in the room. There will also be oxygen, suction and intubation equipment. I will attach below a copy of the section of our protocol that gives details of this equipment.

3) We will have the personnel present to carry out immediate resuscitation. My wife, Ann Mithoefer, BSN, and I will be the therapists for all subjects and will be with them throughout the MDMA sessions. Before doing my psychiatry residency in 1991, I trained in internal medicine at The University of Virginia and was board certified in internal medicine and emergency medicine. I practiced emergency medicine for over 10

years, taught emergency medicine at The Medical University of South Carolina, and was director of two different county emergency rooms and medical director of two county EMS programs during those years. I will maintain Advanced Cardiac Life Support certification during the period of the study. Ann is a registered nurse who has worked in a coronary care step-down unit in the past. Because Ann and I have not treated medical emergencies in recent years, and in order to provide a complete emergency response team, we will hire a currently practicing, board certified, emergency physician and nurse to be in the next room for the first five hours of each MDMA session. They will be familiar with our protocol and with the acute effects of MDMA, and will have no duties other than to be immediately available to respond to any medical emergency in our subjects.

The occurrence of sudden death in an otherwise healthy person taking MDMA would, as you are no doubt aware, almost certainly be due to ventricular fibrillation (VF) or pulseless ventricular tachycardia (PVT). As indicated by the American Heart Association guidelines for treatment of VF or PVT, the most important immediate treatment is defibrillation. The fact that we will have a defibrillator in the room will allow us to institute defibrillation faster than we could in the inpatient clinical research center, where the defibrillator would be on a cart shared by all rooms on the hall. The subsequent implementation of CPR with IV access and intubation would be done with the assistance of the emergency physician and nurse who will immediately come in from the next room. We estimate that this response will be at least 3-5 minutes faster than the response of a "code" team that would have to come from another part of a large university hospital. Once stabilized, any such patient would require monitoring in an ICU and further evaluation. Transfer by ambulance from my office to a nearby hospital would be almost as fast as a trip through the halls and elevators of a university hospital. Most importantly, definitive emergency treatment would be delivered before transfer would be necessary. These precautions were approved by the FDA Neuropsychiatric Division in consultation with their Cardio-renal division. In our telephone conference with FDA physicians Dr. Katz agreed that our outpatient arrangement is probably superior to a hospital research center in terms of patient comfort and safety.

I would appreciate any comments or suggestions you may have about our approach to subject safety. If you would like to talk on the phone, please give me a call at 843-849-6899. Thank you for your interest in what we're doing.

With best regards,

Michael Mithoefer, MD

Here is a section from the protocol detailing emergency equipment:

The office will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. Available emergency medications include antihypertensive agents (such as nitroprusside and labetolol), pressor agents, anxiolytics, and intravenous fluids. In addition to drugs, the crash cart will contain a defibrillator (with telemetry capability), an oxygen tank, a 12-lead electrocardiogram (EKG) device, a suction device, a pulse oxometer, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). We will have equipment for placing an arterial line and monitoring arterial pressure. The researchers have established (in communication with the FDA) contingency plans for responding to those adverse events that appear most likely, based on a comprehensive review of case reports of toxicity in illicit MDMA users (See Appendix). With these personnel and equipment, the researchers would be able to stabilize a patient in the office and then transport them by ambulance if hospital admission were required. The researchers have contacted the Charleston County Emergency Medical Services and learned that, in 2001, the average response time for an ambulance to arrive at a location in the sector of Mt. Pleasant where the research will be conducted was 8 minutes, 55 seconds. Transportation time to the East Cooper Medical Center Emergency Room should take no more than 10 minutes.

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