UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

March 22, 2013

Kristina C. Borror, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

**RE: Serious Non-Compliance concerning the UIC IRB #1 review of UIC IRB protocol #2008-0624**
**Research Protocol # 2008-0624**
**"Affective Neuroscience of Pediatric Bipolar Disorder"**
**Sponsor: National Institutes of Health; Grant #5R01MH081019**
**Principal Investigator: Mani Pavuluri, MD**

Dear Dr. Borror:

In fulfillment of the reporting requirements at 45 CFR 46.103(b)(5), I am writing on behalf of the University of Illinois at Chicago (UIC) Institutional Review Board #1 (IRB00000115) to self-report a determination of serious non-compliance by the IRB. The IRB's determination is in regard to the review of UIC IRB protocol #2008-0624, "Affective Neuroscience of Pediatric Bipolar Disorder," for which Dr. Mani Pavuluri, Director of the Pediatric Mood Disorders Clinic at UIC, is the Principal Investigator.

On March 19, 2013, the IRB Chairs and Executive Chair met to discuss allegations of serious non-compliance against IRB #1. These allegations are the result of findings from a UIC Office for the Protection of Research Subjects (OPRS) internal audit of IRB protocol #2008-0624. These findings include the following:

1. The initial review submission, reviewed at the August 6, 2008 convened meeting, included the NIH and IRB submission application, but lacked a separate research protocol document. The IRB determined that the study could be approved pending minor revisions; in the request for revisions, the IRB indicated that a protocol was required. However, the documentation from the initial convened review did not include the necessary stipulations to support this level of review or guide the expedited reviewer in the review of the protocol. The investigator's response was reviewed and subsequently approved under expedited review procedures.

2. A disclosure of appropriate alternative procedures or courses of treatment was excluded from the informed consent documents by the investigator. The IRB failed to identify this omission during the initial or subsequent continuing reviews of the informed consent documents, assents, and parental permission forms.
3. UIC Amendment #3, approved on April 24, 2009, involved the expansion of the study population to include children ages 10 through 12 years. This amendment was reviewed under expedited review procedures. Since the FDA-approved labeling for the drug used in this study (lithium) does not include children under 12 years of age, the review guide should have documented the rationale for considering that the expansion of the study population to this age group qualified as a minor change in the research; however, no rationale was provided. In addition, the parental permission form did not indicate that lithium was not FDA approved for children under the age of 12.
4. The IRB review should have documented and corrected the multiple inconsistencies between, and within, the research protocol, informed consent documents, parental permissions, assents, initial review application, grant, and other research documents. One example includes the inconsistencies in the protocol requiring subjects to be "medication naïve" versus "lithium naïve," and the eligibility criteria indicating that subjects must have no prior history of psychotropic medication use.

Based on these findings, the Chairs and Executive Chair recommended that IRB #1 be found in serious non-compliance, as the shortcomings reflect violations of the federal regulations and/or have the potential to compromise the integrity of the human subjects protections program.

The Chairs' recommendation and a summary of the allegations of serious non-compliance were presented to IRB #1 for review at the March 20, 2013 convened meeting. The IRB concurred with the Chairs' recommendation and rationale supporting the recommendation, and determined that the findings represent serious non-compliance. The IRB further determined that the following corrective actions should be implemented:

- The IRB review guides and investigator instructions were updated to support UIC's AAHRPP application in 2010. Availability of these guides at the time of the findings in 1-3 above (2008-2009) would have lessened the possibility of these IRB errors occurring. OPRS should continue to re-evaluate the review guides and revise as necessary to ensure their relevance.
- Structure the review process to emphasize the role of the research protocol as the preeminent document describing the research and the supportive role performed by the other submission documents and appendices.
- Develop a series of case studies from the errors found in the current protocol that the Assistant Director for Education and Training will utilize to instruct all 4 UIC IRBs during their April meetings.
- The IRB noted that since 2010 mechanisms for regularly assessing the quality of IRB reviews and appropriateness of the documentation process have been in place. These activities should continue and the findings used to guide continuing education and human subject review activities for the UIC Human Subject Protection Program.
- Lastly, the OPRS will initiate an audit of IRB #1 studies to ensure compliance with the federal regulations related to the required elements of informed consent.

I believe that the actions regarding this issue are being appropriately addressed. We will provide an update on our progress in implementing the above corrective actions. If you have any questions with regard to these matters, please do not hesitate to contact me at (312) 413-8731 or jfischer@uic.edu.

Sincerely,

James H. Fischer, PharmD
Director, Office for the Protection of Research Subjects
Human Protections Administrator, Office of the Vice Chancellor for Research
FWA #00000083

cc: Mitra Dutta, PhD, Vice Chancellor for Research
Clyde Wheeler, PhD, Associate Director, Investigator Outreach and Quality Improvement
Barbara Corpus, CIP, Associate Director, External Relations and Quality Assurance
Patricia West-Thielke, PharmD, Chair, IRB #1

UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Office of the Vice Chancellor for Research (MC 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612

May 22, 2013

Rebecca Claycamp, M.S., CRA
Chief Grants Management Officer
National Institute of Mental Health
6001 Executive Boulevard
Bethesda, MD 20892

**RE: Response to April 23, 2013 NIMH Inquiry for R01MH081019 (Affective Neuroscience of Pediatric Bipolar Disorder); Principal Investigator: Mani Pavuluri, MD, PhD**

Dear Ms. Claycamp:

Thank you for providing the University of Illinois at Chicago (UIC) the opportunity to respond to the issues NIHM raised regarding Dr. Pavuluri's research. It is hoped that the Agency will find the actions taken to date to be satisfactory and reflective of our Institution's commitment regarding the protection of human subjects participating in research at UIC.

Please find the responses to your inquiries outlined in the April 23, 2013 letter addressed below.

1. NIMH seeks an evaluation of the full scale of the reported serious non-compliance in the R01MH081019 study.

   *The responses provided are based on the documentation provided to the auditors in the research records. Due to the lack of or clear documentation contained within the subject records, a definitive response as to a subject's eligibility was often not possible.*

   *The auditors reviewed one hundred and three (103) research records of subjects in the pediatric bipolar disorder (PBD) group. This represented a 100% audit of children with bipolar disorder enrolled in the study. The audit did not extend to the control group of children.*

   How many subjects participated in the non-IRB approved medication washout?

   *Twenty-four (24) subjects participated in the non-IRB approved medication washout. As previously noted, due to the poor study documentation, only an estimate can be provided as to the number of children that had either medication washout or tapering of their pre-study medications.*

How many participants failed to meet the IRB-approved inclusion/exclusion criteria at study entry?

*In total, eighty-nine (89) subjects failed to meet the IRB-approved inclusion/exclusion criteria at study entry. The following list categorizes the PBD subjects by the criteria that were not met. Please note that summation of the list below exceeds 89 as some subjects are listed under multiple categories.*

| ***Inclusion/Exclusion Criteria*** | [redacted] |
|---|---|
| *Psychotropic Medication Naïve* | |
| *Lithium Naïve* | |
| *Suicidal Tendencies* | |
| *Substance Use* | |
| *History of Seizures* | |
| *Age* | |
| *Missing WASHU-KSADS (used to establish PBD diagnosis)* | |

How many children younger than age twelve were administered off-label lithium as part of their study participation, and what were their respective ages?

*Thirty-three (33) children younger than age twelve were enrolled in the research. As the research records did not include medication logs, it is unknown whether the children were administered off-label lithium as part of their study participation. The respective ages of the children younger than twelve are as follows:*

| ***Age*** | [redacted] |
|---|---|
| *8* | |
| *9* | |
| *10* | |
| *11* | |

Did any of the under-twelve aged participants experience a serious adverse event attributable to the study drug? Please provide assurance that appropriate clinical care was provided, as warranted.

*No information was included in the research records or reported to the IRB indicating the occurrence of a serious adverse event.*

2. Regarding the off-label administration of lithium to participants younger than age twelve in R01MH081019, did the UIC IRB determine whether an Investigational New Drug Application (IND) should have been filed with the Food and Drug Administration (FDA) of if the study was IND Exempt? If the UIC finds that a lapse of compliance occurred with FDA regulations (21 CFR Part 312), the NIMH asks to be informed of any corresponding notification to the FDA and study subjects.

*In accord with 21 CFR 312.2(b)(1), the UIC IRB had determined that the off-label administration of lithium to participants younger than age twelve in this protocol (10 -11 years old) was exempt for the submission of an IND to the FDA. Based upon the literature and current clinical practice, the IRB determined that the use of lithium in this subject population had met all six of the following conditions:*

*(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;*

*(ii) it is not intended to support a significant change in the advertising for the product;*

*(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;*

*(iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];*

*(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and*

*(vi) it does not intend to invoke 21 CFR 50.24.*

3. [redacted] The NIMH strongly encourages the UIC to address this important issue in institutional guidance and training provided to UIC Institutional Review Boards that oversee NIH-supported research.

*The UIC Office for the Protection of Research Subjects (OPRS) is reviewing and will be revising the UIC policy and guidance regarding the requirements for and composition of a DSMB. These revisions will ensure that UIC policy concurs with the NIH and NIMH policies for Data and Safety Monitoring. Once the revised policy is approved, an appendix for collecting information related to the composition and function of the proposed or IRB-required DSMB will be used as a tool to operationalize the policy. Implementation and IRB training are scheduled for June 2013.*

*It should be noted that the research protocol as presented and as approved by the IRB did not involve a high-risk intervention, i.e. medication washout. Therefore, in accord with the NIMH guidance and UIC policy on data safety monitoring, an independent DSMB was not required.*

> ***NIMH Policy on Data and Safety Monitoring in Extramural Investigator-Initiated Clinical Trials,*** *" For small-scale, single-site, NIMH-supported clinical trials, independent DSMBs may not be necessary, especially when the risk of the intervention(s) is considered relatively low. In most such studies, the Principal Investigator (PI) would be expected to perform the monitoring function as part of the general oversight and scientific leadership of the study. The PI must comply with requirements (see summary below) for prompt reporting of study-related toxicity and of any unanticipated problems involving risks to subjects or others. "*
> *(http://www.nimh.nih.gov/funding/grants/nimh-policy-on-data-and-safety-monitoring-in-extramural-investigator-initiated-clinical-trials.shtml)*

*The DSMP submitted as part of the grant application to NIMH and reviewed by the IRB also did not include an independent DSMB.*

*The above statements are not meant to defend the lack of independence of the DSMB for this study. Once the IRB had approved the investigator's data safety monitoring plan involving the oversight of the DSMB, the DSMB should have been appropriately composed. The above points were, however, raised to show our recognition of the difficulties that arise during the evaluation of the Data Safety Monitoring plan and the need for accurate communication between the IRB and investigator.*

4. The April 8, 2013 report of serious non-compliance indicates that the head of the UIC Department of Psychiatry will develop a Standard Operating Procedures (SOP) establishing a process to ensure a clear distinction between clinical and research activities. The NIMH strongly recommends that this SOP address the distinct roles of clinician and researcher with regards to recruitment and consent activities.

*Dr. Anand Kumar, the Head of the UIC Department of Psychiatry, developed the following SOP to ensure that clinical investigators in the department are aware of the need and put into place appropriate measures to distinguish between their clinical and research roles. This SOP was reviewed and accepted by the Director of the UIC Office for the Protection of Research Subjects and Executive IRB Chair.*

**********

***University of Illinois at Chicago Department of Psychiatry***
***Standard Operating Procedure: Avoiding Conflicts When Investigators May Serve as Both Investigator and Clinician for Potential Research Subjects***

*Principal Investigators and Co-Investigators in the Department of Psychiatry will be informed by the Department Head of the importance of this issue and instructed to amend, as appropriate, active and new research protocols pertaining to clinical research involving patients.*

*"When recruiting potential research subjects from amongst their own patients and/or from patients in clinical program under their direction, Principal Investigators must consider the above dual investigator-clinician role for both the PI and for all Co-Investigators. All investigators must consider the possibility that their patients may feel obligated to participate and/or that patients may worry that their clinical care may be affected if they were to enroll or not enroll in the investigator-clinician research protocol. If a dual role exists in which an investigator is also the treating clinician of the subject-patient, the Principal Investigator should disclose this dual role and possible conflict of interest to subjects within the consent form. Moreover, investigators should reinforce in the consent form with their patients that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future.*

*A sample of such language is provided: "Your mental health care provider may be an investigator of this research protocol, and as an investigator, is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another clinician who is not associated with this project. You are not obligated to participate in any research project offered by your clinician. Your participation in this research study is voluntary and you do not have to participate. The decision to not participate will not affect your clinical care now or in the future."*

*During the IRB review of clinical trials from the Department of Psychiatry, the need for an independent consent monitor or subject advocate will be evaluated. The vulnerability of the population, high risk intervention, an investigator held IND, and investigator compliance record will be considered by the IRB in making this determination.*

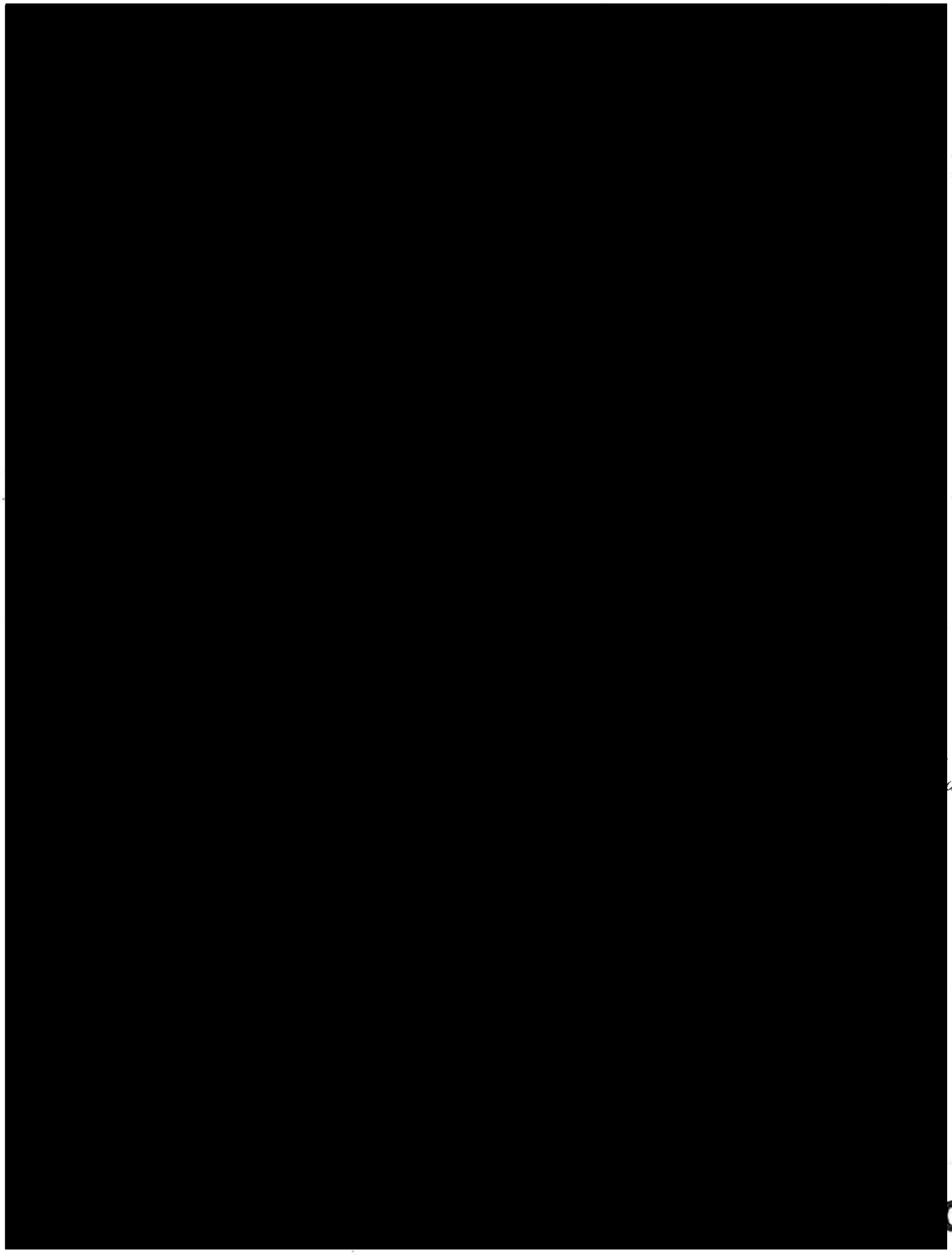
5. The April 8, 2013 report of serious non-compliance also indicates that "Dr. Pavuluri must be removed as Principal Investigator from all research protocols." Have the research protocols, and projects associated with, Dr. Pavuluri's two other NIMH grants – R01MH85639-04 and K24MH096011-02 – been evaluated for noncompliance and, if so, were there any findings? (A separate letter is being sent to Mr. Luis Vargas, Executive Director, Office of Research Services, to determine the current status of each of Dr. Pavuluri's grants.)

[redacted]

[redacted] *Both studies remain suspended as determined on April 3, 2013 and April 9, 2013, respectively.*

*The draft audit results are provided below.*

[redacted]



[redacted]

6. The March 22, 2013 report to OHRP indicates that the UIC will initiate an audit of studies overseen by IRB #1 to ensure compliance with 45 CFR Part 46.116 (required elements of informed consent). Please notify the NIMH of subsequent findings associated with this audit and any other official communication to or from the OHRP pertaining to the corrective action plans outlined in the March 22, 2013 or April 8, 2013 reports of serious non-compliance.

   *An audit of UIC Institutional Review Board (IRB) #1-approved studies was conducted to ensure compliance with the federal regulations related to the required elements of consent (45 CFR 46.116 and/or 21 CFR 50.25). The auditors reviewed the IRB #1 meeting agendas between February 2012 and January 2013 to compile a list of initial review submissions. The list of initial review submissions was then limited to protocols which received approval and have not since been closed. The final approved consent or consent/authorization was audited on the greater than minimal risk IRB#1 research protocols.*

   *The follow-up letter to OHRP regarding the IRB #1 serious non-compliance has been included for your reference.*

Please also be aware that Dr. Pavuluri received notification from the UIC Research Integrity Officer of allegations of possible research misconduct associated with grant # RO1MH081019; and that the matter has been referred for Inquiry. The process for evaluating such allegations is described in the University of Illinois *Policy and Procedures on Integrity in Research and Publication.* This policy may be accessed at http://www.vpaa.uillinois.edu/policies/Integrity-Policy.pdf.

We want to reiterate our Institution's commitment to the protection of human subjects participating in research at UIC and trust that we have conveyed this in our response.

Please feel free to contact me at 312-413-8731 or jfischer@uic.edu should you have further questions or require any additional information.

Once again, thank you for providing us with the opportunity to respond to this important inquiry.

Sincerely,

James H. Fischer, PharmD
Director, Office for the Protection
of Research Subjects
Human Protections Administrator
FWA #00000083

Mitra Dutta, PhD
Vice Chancellor for Research
UIC Distinguished Professor, Department of
Electrical and Computer Engineering

cc: Patricia West-Thielke, PharmD, Chair, IRB #1
Dimitri Azar, MD, Dean, College of Medicine
Anand Kumar, MD, Head, Department of Psychiatry
Mani Pavuluri, MD, Principal Investigator

Attachments: Follow-up Letter to OHRP regarding IRB #1 Serious Non-Compliance, dated May 16, 2013

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
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September 23, 2015

Kristina C. Borror, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

**RE: Final IRB Corrective Actions Following Notification of Findings from Research Misconduct Investigation**

**University of Illinois at Chicago Research Protocol #2008-0624**
**"Affective Neuroscience of Pediatric Bipolar Disorder"**
**Sponsor: National Institutes of Health; Grant #5R01MH081019**
**Principal Investigator: Mani Pavuluri, MD**

**University of Illinois at Chicago Research Protocol #2009-1022**
**"Developing Brain Function in Adolescent Bipolar Disorder"**
**Sponsor: National Institute of Mental Health; Grant #5 R01 MH085639-04**
**Principal Investigator: Mani Pavuluri, MD**

**University of Illinois at Chicago Research Protocol #2011-0654**
**"Brain Networks Modulating Affect Self-Regulation in Pediatric Mania"**
**Sponsor: National Institute of Mental Health; Grant #5 K24 MH09601116-02**
**Principal Investigator: Mani Pavuluri, MD**

Dear Dr. Borror:

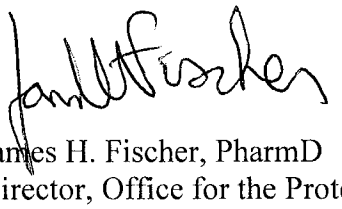
This communication is a follow-up notification of actions taken by the University of Illinois at Chicago (UIC) Institutional Review Board #1 (IRB00000115) regarding the IRB's serious noncompliance determinations related to the above-named research protocols, conducted by Dr. Mani Pavuluri, Professor and Director of the Pediatric Mood Disorders Clinic at UIC. Previous communications concerning these incidents of serious noncompliance were provided to the Office for Human Research Protections on the following dates:

[redacted]

The IRB acknowledged the Investigation Panel's findings. The IRB was also informed that the UIC Chancellor has reviewed the findings, and has implemented an immediate and indefinite revocation of all research rights and privileges, including any advisory roles or participation as key research personnel. The IRB concurred with the Chancellor's determination and specifically revoked the investigator's privileges to conduct research involving human subjects until research privileges are restored by the Chancellor. At that time, the IRB will re-assess the investigator's qualifications to conduct human subject research. In addition, the Chancellor has determined that the Investigator must make an immediate retraction of the three publications cited by the Investigation Panel. It was noted that any sanctions on the Investigator's clinical privileges will be at the discretion of the Dean of the College of Medicine. The IRB was further notified that a complete report of the UIC RIO investigation would be submitted shortly to the DHHS Office of Research Integrity.

I believe that the issues identified with the serious noncompliance and research misconduct have been addressed appropriately. If you have any questions, please contact me at (312) 413-8731 or jfischer@uic.edu.

Sincerely,



James H. Fischer, PharmD
Director, Office for the Protection of Research Subjects
Human Protections Administrator, Office for the Vice Chancellor for Research
Executive Chair, UIC IRB
FWA #00000083

cc: Mitra Dutta, PhD, Vice Chancellor for Research
Clyde Wheeler, PhD, Associate Director, Investigator Outreach and Quality Improvement
Barbara Corpus, CIP, Associate Director, External Relations and Quality Assurance
Mark Grabiner, MD, Research Integrity Officer
Patricia West-Thielke, PharmD, Chair, IRB #1
Dmitri Azar, MD, Dean, College of Medicine
Anand Kumar, MD, Head, Department of Psychiatry
Mani Pavuluri, MD, PhD, Principal Investigator
Marjorie A. Garvey, Program Officer, National Institute of Mental Health

UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Office for the Protection of Research Subjects (MC 672)
Office of the Vice Chancellor for Research
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October 26, 2015

Kristina C. Borror, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

**RE: Clarification of Statements in Final IRB Corrective Actions Letter of September 23, 2015**

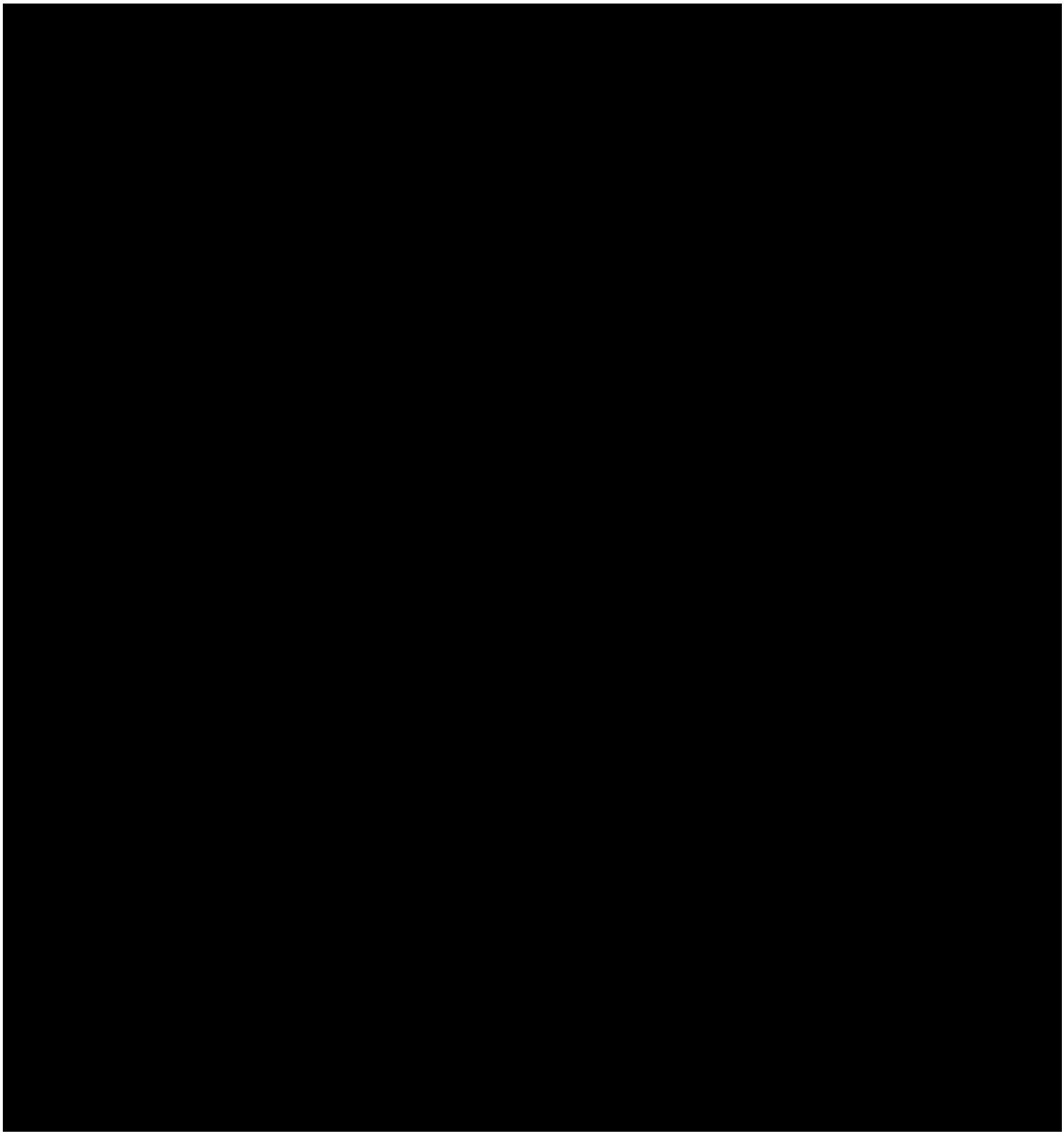
**University of Illinois at Chicago Research Protocol #2008-0624**
**"Affective Neuroscience of Pediatric Bipolar Disorder"**
**Sponsor: National Institutes of Health; Grant #5R01MH081019**
**Principal Investigator: Mani Pavuluri, MD**

**University of Illinois at Chicago Research Protocol #2009-1022**
**"Developing Brain Function in Adolescent Bipolar Disorder"**
**Sponsor: National Institute of Mental Health; Grant #5 R01 MH085639-04**
**Principal Investigator: Mani Pavuluri, MD**

**University of Illinois at Chicago Research Protocol #2011-0654**
**"Brain Networks Modulating Affect Self-Regulation in Pediatric Mania"**
**Sponsor: National Institute of Mental Health; Grant #5 K24 MH09601116-02**
**Principal Investigator: Mani Pavuluri, MD**

Dear Dr. Borror:

This communication is a clarification of the statement, "…subsequent reports received from the parents of subjects and a preponderance of evidence…", requested by you on October 8, 2015 in follow-up to our communication with OHRP on September 23, 2015. [redacted]



UIC

These communications have been reviewed by the UIC IRB. As the three studies were suspended in Spring, 2013 and terminated in Spring, 2014 and the investigator suspended from conducting human subject research since April, 2013, the IRB determined that no additional actions were required.

As the Complainant in this case, the IRB's knowledge of the Investigative Panel's actions are limited to the executive summary provided by the UIC RIO. Other than the parent and subject communication log, I am not party to other evidence nor the rationale for the conclusion made by the Investigative Panel. The statement, "Although the Investigator has repeatedly claimed that no subjects were harmed in her studies, the Investigation Panel believes that these claims are false based on subsequent reports received from the parents of subjects and a preponderance of evidence to the contrary", in our September 23rd letter was extracted from the executive summary of the Investigative Panel report. However, we neglected to include the following elaboration that places the statement in its appropriate context, "It is clear that it is not because of the Respondent's actions that harms may have been avoided. It is despite

her actions that no subject came to worse harm. These events go to the very heart of the conduct of clinical research, and underscore the role and value of IRB and ORI processes and federal regulations in the protection of human subjects and ensuring the integrity of the research data." Placing the statement in this context does clarify the Investigative Panel's conclusion.

I believe that the additional information provided in this letter clarifies the statement cited in your October 8, 2015 e-mail. If you have any questions, please contact me at (312) 413-8731 or jfischer@uic.edu.

Sincerely,

James H. Fischer

James H. Fischer, PharmD, FCCP
Director, Office for the Protection of Research Subjects
Human Protections Administrator, Office for the Vice Chancellor for Research
Executive Chair, UIC IRB
FWA #00000083

## Corpus, Barbara Ann

**From:** Johnston, Teresa D.
**Sent:** Friday, November 06, 2015 2:31 PM
**To:** IRPT.OS@hhs.gov
**Cc:** Fischer, James H; Corpus, Barbara Ann; Cortes, Nora Elena
**Subject:** Clarification of Statements in Final IRB Corrective Actions
**Attachments:** Clarification of Statements in Final IRB Corrective Actions 2008-0624 2009-1022 2011-0654 10.26.2015.doc

To whom it concerns,

Please find attached a Clarification of Statements in the Final IRB Corrective Actions letter of September 23, 2015, as related to UIC (FWA#00000083) protocols #2008-0624, #2009-1022, and #2011-0654. This Clarification of Statements is in response to a request from Dr. Kristina Borror for additional information, per her email dated October 8, 2015.

Please note that the attached letter was also sent as a hard copy via USPS certified mail on October 29, 2015, and that this email is a follow-up to that communication. OPRS apologizes for any confusion or inconvenience caused if these communications have been sent incorrectly, as they were processed by a staff member who was asked to send the letters in my absence.

Regards,

Teresa

Teresa D. Johnston, B.S., C.I.P.
Assistant Director
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University of Illinois at Chicago
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UNIVERSITY OF ILLINOIS
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April 8, 2013

Kristina C. Borror, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

**RE: Determination of Serious Non-Compliance**
**University of Illinois at Chicago Research Protocol # 2008-0624**
**"Affective Neuroscience of Pediatric Bipolar Disorder"**
**Sponsor: National Institutes of Health; Grant #5R01MH081019**
**Principal Investigator: Mani Pavuluri, MD**

Dear Dr. Borror:

This communication is a follow-up to my letter of March 12, 2013 informing OHRP of the suspension of research activities for the protocol "Affective Neuroscience of Pediatric Bipolar Disorder". Consequently, the University of Illinois at Chicago (UIC) Institutional Review Board #1 (IRB00000115) has made a determination of Serious Non-Compliance for this research study. Dr. Mani Pavuluri, Professor and Director of the Pediatric Mood Disorders Clinic at UIC, is the principal investigator.

Briefly, UIC IRB #1 suspended approval for this protocol at the March 6, 2013 meeting after determining that a subject described in a Prompt Report, received on January 18, 2013, underwent a medication washout prior to receiving study medication (Lithium). A medication washout was never approved by the IRB. At the April 3, 2013 convened meeting, the IRB reviewed the results of an internal audit that was requested following the suspension of IRB approval for Protocol 2008-0624. The original charge to the auditors was to assist the IRB in understanding whether: 1) subjects enrolled in this study underwent a medication washout regimen, 2) subjects were medication naïve or lithium naïve at study entry, and 3) subjects had been exposed to any psychotropic medication in their lifetime. This charge was expanded once the Office for the Protection of Research Subjects (OPRS) administration was made aware of auditor observations of a wider range of deficiencies.

The IRB determined that the following findings from the audit report represented serious non-compliance:

- **Failure of the principal investigator to appropriately distinguish her clinical and research activities, primarily related to the medication washout.** According to the investigator, subjects were prescribed medication washouts for clinical care purposes. However, the occurrence of the washouts while subjects were participating in the trial and research record notations from research staff, parents and subjects provide the perception that it occurred as a component of the research. A medication withdrawal was not part of the IRB approved protocol.
- **Failure to follow the eligibility criteria specified in the IRB approved protocol.** The investigator enrolled subjects who were outside the criteria approved by the IRB for participation in the study for one or more of the following: age range, concurrent medications, lithium naïve, use of any psychotropic medication in subject's lifetime, history of seizures, current or history in past three (3) months of a diagnosis of substance abuse/dependence or use of illicit drugs or alcohol in past three (3) weeks, and history of self-mutilation and suicidality.
- **Failure to follow the IRB-approved protocol during the conduct of the study.** The auditors identified the performance of several assessments that were not included in the IRB-approved protocol, as well as the failure to perform some procedures described in the protocol.
- **Deficiencies in the Informed Consent, Assent, and Authorization Forms:** These included handwritten changes made to the documents without IRB approval, corrections made in an improper manner (e.g., white out used, initials and dates not provided to allow attribution), consent for optional procedures not properly completed, and use of consents without the IRB approval stamp.
- **Deficiencies in Study Documentation:** Global observations from the audit report included missing source documentation and data collection forms, widespread lack of attribution, improper data correction methods, dates and subject IDs missing beyond the first page on multi-page instruments and questionnaires, and duplicate original source documents.

The findings described above were determined to represent Serious Non-Compliance as they increase the potential risks of harm to the rights and welfare of the subjects; affect the validity of the research data; and compromise the integrity of the human subject protection program.

The IRB is requiring the following corrective actions related to:

**Principal Investigator**

- Effective immediately, Dr. Pavuluri must be removed as Principal Investigator from all research protocols.
- Dr. Pavuluri's privileges to serve as a Principal Investigator in human subject research at UIC are suspended for a minimum period of six months.
- After six months and the completion of the corrective action plan described below, this suspension of research privileges will be evaluated by the UIC IRB#1.

- After initial restoration of Dr. Pavuluri's research privileges and for a minimum period of six months, she will be allowed to function as a Principal Investigator on research protocols under the direct oversight of an experienced Principal Investigator. Selection of the experienced investigator will be agreed upon by the Department Head of Psychiatry and the UIC IRB#1.
- If, after a minimum period of one year from the initial suspension, Dr. Pavuluri continues to demonstrate compliance with the Human Subject Protection Program (HSPP) regulations, full research privileges as a Principal Investigator will be restored.
- Before the reinstatement of Dr. Pavuluri's privileges as a Principal Investigator, she must understand and implement within her clinical research program Good Clinical Practice (GCP) regulations and guidelines. Evidence of this will be provided by the following:
  - Dr. Pavuluri and key members of her research group must complete the following training programs: 1). GCP Overview (e.g., CITI GCP or NIAID GCP module); 2). Principal Investigator Oversight and Responsibilities (refer to page 114 of the Barnett Educational Services for example courses); and 3) the GCP training series to be presented to Department of Psychiatry faculty by the OVCR.
  - Dr. Pavuluri must implement appropriate procedures to ensure that her research program operates according to GCP and UIC HSPP standards, including GCP mandated Standard Operating Procedures (SOPs). Patricia Fischer, R.N., CCRP, is assigned to oversee this process with Dr. Pavuluri and her staff. Dr. Pavuluri is also required to submit the SOPs and other supporting documentation (e.g., case report forms, eligibility checklists, delegation and training logs, etc.) to the IRB as evidence of the implementation of procedures supporting GCP and UIC HSPP standards.
  - Dr. Pavuluri must re-submit UIC IRB Protocol 2008-0624 for IRB review. This submission must include a research protocol that provides an accurate, complete and organized delineation of the study procedures, as well as informed consent documents that thoroughly describe the procedures and risks involved with study participation. Clyde Wheeler, Ph.D., Associate Director for Investigator Outreach and Compliance, will assist Dr. Pavuluri with this process.
  - During the suspension and before the reinstatement of her privileges as a Principal Investigator, Dr. Pavuluri must attend a minimum of six IRB meetings of either UIC IRB#1 or IRB#3.

In addition to the above corrective actions for the Principal Investigator, the IRB is requiring the following corrective actions related to:

**Currently active research protocols**

- The co-investigators on Dr. Pavuluri's greater than minimal risk and minimal risk studies will be notified of the Serious Non-Compliance and suspension of the research.
- Research activities for both greater than minimal risk and minimal risk studies are suspended until Dr. Pavuluri's clinical research privileges have been restored. During this time, a "caretaker" Principal Investigator (PI) will be appointed by the Department Head of Psychiatry to oversee administrative matters. Dr. Pavuluri should have no primary involvement; however, the "caretaker" PI may consult with her, as needed, to protect the rights and welfare of subjects. Sponsors should be notified of this change by the Department of Psychiatry.

- Subjects who participated in IRB Protocol 2008-0624 are to receive a letter notifying them to contact the "caretaker" PI, or other individual delegated by the "caretaker" PI, if they have questions about study participation during the time that Dr. Pavuluri's involvement has been suspended. The OPRS, Department of Psychiatry and UI University Counsel will collaborate in drafting an appropriate notification letter.
- Since none of the suspended studies are therapeutic trials and no subjects are currently enrolled in the greater than minimal risk protocols, the IRB does not believe that their suspension for at least 6 months will harm or deny direct benefit to subjects. The IRB, however, welcomes the Department Head to refute this judgment and request the re-opening of any of the suspended studies under a new Principal Investigator.
- With the exception of IRB Protocol 2008-0624, the IRB may allow data analysis to occur with the other protocols following submission of an amendment to the IRB requesting continuation of data analysis. The data analysis will occur under the supervision of the "caretaker" PI. The amendment should include a letter from the "caretaker" PI assuring the IRB that the research study is in a reasonable state, that all subjects were consented in an appropriate and IRB-approved manner, and that the data were collected in an appropriate and IRB-approved manner.

**Integrity of the research data**

- The Research Integrity Officer (RIO) will be asked to evaluate the integrity and scientific validity of the data as a result of: 1) enrollment of subjects failing to meet the eligibility criteria (and thus adding confounding variables to the analysis) and 2) inconsistent documentation, poor attribution, missing data and unacceptable data correction methods in the source documentation.
- The IRB has determined that all data related to protocol 2008-0624 must be censored and cannot be used for publication. In addition, the data must be permanently secured.

**Department of Psychiatry**

- The Department Head is responsible for ensuring that the Department develops an SOP for clinical investigators that establishes a process to ensure that a clear distinction exists between their clinical and research activities. The SOP is to be submitted to the IRB by June 1, 2013. The SOP should be communicated to all investigators in the Department who have clinical responsibilities.
- The Department should coordinate with OPRS to provide a Basic GCP and Investigator Responsibilities seminar for clinical investigators within the Department of Psychiatry. OPRS will provide this seminar on two occasions. The Department of Psychiatry will provide OPRS with a list of individuals subject to this requirement. New, non-exempt protocol submissions will not be accepted from Department of Psychiatry investigators who do not attend one of the sessions by August 15, 2013.

**Institution**

- The OPRS will work to increase the number of not for cause audits of clinical investigators, aiming for one (1) per month.
- The Office of the Vice Chancellor for Research (OVCR) and College of Medicine will establish a quality assurance (QA) program to provide clinical monitoring of UIC conducted clinical trials. The QA program will focus on research sponsored by the

National Institutes of Health (NIH) and other non-Pharma funded clinical trials. Other selection criteria will include investigator experience, history of previous compliance problems, number and type of participants, expected recruitment, and complexity of research. This program has a tentative implementation date of October 15, 2013.

- The Executive IRB Chair will contact the leadership at the National Institute of Mental Health (NIMH), sponsor of protocol 2008-0624, for their input on the proposed corrective actions.

I believe the concerns related to non-compliance are being appropriately addressed per the corrective action plan as described above. I will provide a follow-up report updating you on our progress in addressing this problem.

If you have any questions, please contact me at (312) 413-8731 or jfischer@uic.edu.

Sincerely,

James H. Fischer, PharmD
Director, Office for the Protection of Research Subjects
Human Protections Administrator, Office for the Vice Chancellor for Research
Executive Chair, UIC IRB
FWA #00000083

cc: Mitra Dutta, PhD, Vice Chancellor for Research
Clyde Wheeler, PhD, Associate Director, Investigator Outreach and Quality Improvement
Barbara Corpus, CIP, Associate Director, External Relations and Quality Assurance
Patricia West-Thielke, PharmD, Chair, IRB #1
Dmitri Azar, MD, Dean, College of Medicine
Anand Kumar, MD, Head, Department of Psychiatry
Mani Pavuluri, MD, Principal Investigator
Marjorie A. Garvey, Program Officer, National Institute of Mental Health