DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 240-453-8328
FAX: 240-453-6909
E-mail: Karena.Cooper@hhs.gov

December 19, 2007

Christopher Heller, MD
Acting Chief Medical Officer
Carondelet Health Network
1601 W. St. Mary's Road
c/o Quality Management Office
Tucson, AZ 85745

RE: Human Research Protections Under Federalwide Assurance FWA-5710

Research Project: Post Partum Depression Studies
Principal Investigator: Carole P. Sheehan, M.A., R.N.C.
Protocol Number: #163 and #198

Dear Dr. Heller:

The Office for Human Research Protections (OHRP) has reviewed the Carondelet Health Network's (CHN's) May 15, 2007 and November 13, 2007 reports regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research.

Based upon its review of CHN's reports, OHRP makes the following determinations regarding the above-referenced research:

(1) It was alleged that the approvals of protocols #163 and #198 were terminated by the CHN institutional review board (IRB) and notice of those terminations was not promptly reported to the principal investigator, nor were the reasons for the terminations reported to the principal investigator.

From the information provided to OHRP, it appears that protocol #198 was not approved by the IRB.

With regard to protocol #163, CHN stated in its May 15, 2007 report to OHRP that the CHN IRB on November 7, 2006 voted to terminate study #163 for continued noncompliance with IRB directives.

A timeline included in the materials sent to OHRP included the following entry - Aug. 14, 2006: "Dr. Marsteller submits a memo to CHN administration stating that the post-partum depression studies had been suspended due to nonconformities and mischaracterization of the status of study #163." The minutes from the September 5, 2006 IRB meeting contain the following statement: "The study was suspended by the chairman effective August 23, 2006 due to a series of inconsistencies in documentation and communication with the investigator…Recommendation: Suspend study at this time. Notify the investigators of this suspension through CHN Administration."

The timeline also included the following entry - September 1, 2006: A meeting is held with…<principal investigator and others> to discuss the status of these studies…They are also informed that the study is formally suspended until the IRB meets and makes a decision on the disposition of the study…..

OHRP notes that the minutes from the November 7, 2006 IRB contain the following entry:

> "Issues and their resolution: The committee discussed this study with regard to the continued noncompliance with IRB instruction. A letter will be sent to OHRP notifying them of the termination of the study. The investigator will also be notified."

CHN sent an incident report to OHRP dated December 5, 2006, stating:

> Reason for termination – This study is being terminated because of continued noncompliance with IRB requirements and breaches in procedures as to the governing regulations on HSP. This IRB had previously on several occasions temporarily suspended the study until the investigators returned the study to compliance. The termination of this study was finally necessitated when the investigators subsequently made false and misleading statements to the IRB as to the status of the human subjects enrolled in this study.

The principal investigator received a notification email from the IRB on December 6, 2006 that the study had been terminated at an earlier date. That email stated only the following: "Just to let you know that the OHRP requires the IRB to give them notification when a study is terminated. As there is also a time frame for

this notification, we thus today notified OHRP that the PPD study had been previously terminated."

On December 20, 2006, the principal investigator sent a letter to the IRB in which she requested that the IRB send her a note indicating the date of termination and how that determination was made.

The January 9, 2007 IRB minutes include the following statement: "…it was recommended that a letter be sent to the Principal Investigator for the study stating that the study was terminated. They were not formally notified by the IRB however, they had been verbally notified of the suspension of the study." The IRB sent a letter to the principal investigator dated January 10, 2007 that stated the following:

> In follow-up to our recent meeting of the CHN Human Subjects Committee we learned that you had not been formally notified of the termination of this study. We had understood that CHN administration would be carrying out that notification. Since this has not been done formally as yet, I am hereby notifying you that this study was terminated on September 9, 2006 as a result of our meetings with CHN legal. This termination was a result of continued noncompliance with IRB recommendations and federal regulations. It is with regret that we also notified the OHRP of this termination. The regulations make it mandatory for us to do so. A copy of that letter is enclosed."

OHRP notes that it is unclear why the letter to the principal investigator references September 9, 2006 as the date of termination of the study, when other materials sent to OHRP reference November 7, 2006 as the termination date.

OHRP notes that approval of study #163 was terminated by the CHN IRB on November 7, 2006, and the principal investigator was given official notice of the termination on January 10, 2007. OHRP is unable to substantiate the allegation that the IRB did not promptly notify the principal investigator of the termination of study #163.

(2) OHRP finds that CHN does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(b) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(c) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

OHRP also has the following additional concern regarding protocol #163:

(3) [Redacted]

OHRP offers the following additional guidance:

(4) OHRP notes that the CHN policy entitled "Human Subjects Committee Risk Evaluation" contains the following statement: "Behavioral studies, nutrition studies, observational studies, surveys, or questionnaires would be considered minimal risk." OHRP notes that there are circumstances in which the types of studies listed in the above statement may entail more than minimal risk to subjects. OHRP advises that this statement be revised accordingly.

(5) OHRP notes that the CHN policy entitled "Human Subjects Committee Informed Consent" contains the following statement: "The IRB can waive the use of a consent form or consent documentation for certain research, e.g., studies utilizing questionnaires in which responding to a questionnaire signifies implied consent."

Except for certain emergency research, there are only two circumstances under which the regulations give IRBs authority to waive the requirements for obtaining informed consent of subjects. The first waiver authority is applicable only to research activities designed to study certain aspects of public benefit or service programs; the conditions under which this waiver may be authorized by an IRB are detailed at 45 CFR 46.116(c). The second

waiver authority is described at 45 CFR 46.116(d) as follows: an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
(a) the research involves no more than minimal risk to the subjects;

(b) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(c) the research could not practicably be carried out without the waiver or alteration; and

(d) whenever appropriate, the subjects will be provided with additional information after participation.

The regulations do not provide a mechanism for "implied consent." OHRP suggests that the above policy be revised to more accurately reflect HHS regulations at 45 CFR 46.116(d).

(6) OHRP notes that the CHN policy entitled "Human Subjects Committee Procedural Guidelines" contains the following statement: "Informed consent will be legally sufficient and meet the FDA requirements for acceptable written consent forms." OHRP notes that that while HHS regulations are referenced by number at the end of this policy, the statement referenced does not refer to OHRP or HHS regulations. OHRP suggests that the above referenced policy be revised to include references to OHRP and HHS regulations where appropriate.

(7) OHRP notes that the CHN policy entitled "Human Subjects Committee Reporting Requirements" lists the following as the purpose of the policy: "The Investigator must promptly report in writing any changes in research protocol or consent form and all serious adverse events (SAEs) to the IRB." OHRP notes that this policy omits any reference to the required reporting to OHRP referenced in 45 CFR 46.103(a) and 46.103(b)(5). It also fails to include any reference to unanticipated problems involving risks to subjects or others, as well as the requirement that serious or continuing noncompliance, suspensions and terminations should be reported to OHRP and the sponsor. OHRP suggests that the above referenced policy be revised to include references to OHRP and HHS regulations where appropriate.

(8) OHRP notes that the CHN policy entitled "Human Subjects Committee Function and Purpose" contains the following statement in section IV, #5: "The IRB will be responsible for reporting to CHN Chief Medical Officer any unanticipated problems involving risk to human subjects, serious or continuing noncompliance with FDA regulations and/or IRB policy, leading to a determination by the IRB to suspend or terminate a study. This shall occur in cases when the IRB determines that the issues are egregious enough to warrant suspension or termination of the study." OHRP notes that this policy omits any reference to reporting requirements to OHRP required in 45 CFR 46.103(a) and 46.103(b)(5). OHRP suggests that the above referenced policy be revised to include references to OHRP and HHS

regulations where appropriate.

Please submit your responses to the above findings and concerns so that OHRP receives them no later than February 15, 2008.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Karena Cooper, J.D., M.S.W.
Division of Compliance Oversight

cc: Dr. Chris Arslanian, IRB Coordinator, CHN
Dr. Lawrence Marsteller, IRB Chair, CHN IRB
Ms. Carole P. Sheehan, CHN
Dr. Ivor Pritchard, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Kelley Booher, OHRP
Mr. Barry Bowman, OHRP