DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 19, 2005

Dr. Michael M. Gottesman
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room160
1 Center Drive
Bethesda, MD 20892

RE: Human Research Subject Protections Under Federalwide Assurance FWA-5897

Dear Dr. Gottesman:

OHRP has reviewed your September 23, 2005 response to OHRP's August 25, 2005 letter containing findings, concerns and recommendations following OHRP's site visit at the National Heart, Lung, and Blood Institute (NHLBI) in July. OHRP notes that NHLBI has taken the following corrective actions in response to the findings and concerns discussed in OHRP's August 25, 2005 letter:

> (1) OHRP found that the NHLBI IRB granted numerous extensions of time to conduct continuing review beyond the expiration of IRB approval, in violation of Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e). OHRP also found that the NHLBI IRB conducted continuing review after the expiration date for several protocols, when extensions of time were neither sought nor granted.
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> **Corrective Action:** OHRP acknowledges that NHLBI revised its continuing review procedures consistent with those approved for all NIH IRBs by the Human Subjects Research Advisory Committee (HSRAC) at its September 9, 2005 meeting. All NHLBI protocols must complete continuing review and approval within 365 days. For any protocol that has not completed this process by the continuing review date, IRB approval expires automatically. All research activities must stop, including new subject accrual. In the rare circumstance when review is not completed by the continuing review date and when it is in an enrolled subject's best interest to continue to receive research interventions, the primary investigator must submit to the IRB a memo justifying this continuation. The convened IRB must approve the request. Continuation may occur only for the brief period required to complete the review process and the period must be specified by the IRB. The next continuing review date for a protocol will be set by the

date the convened IRB approves the protocol.

(2) Under HHS regulations at 45 CFR 46.115(a), an institution or an IRB must maintain adequate documentation of IRB activities, including copies of all correspondence between the IRB and investigators. OHRP found that in the protocol files OHRP examined during its on-site visit at NHLBI, the site visit team often had difficulty determining the dates of all IRB actions related to the review and approval of the protocols, particularly when the convened IRB approved protocols with multiple stipulations requiring detailed responses from investigators.

Corrective Action: OHRP acknowledges that NHLBI has developed standard templates for initial and continuing review approvals. These standard forms will be sent to the principal investigators and research coordinators to inform them of the date on which the IRB approved their protocols, and will indicate the date IRB approval expires. Copies of these notices will be maintained in each protocol file. All correspondence with the investigator will be clearly dated and maintained in the IRB protocol file. The expiration date for protocols will be set by the date the convened IRB approves the protocol.

(3) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research, IRBs determine that risks to subjects are minimized and are reasonable in relation to anticipated benefits. HHS regulations at 45 CFR 46.111(a)(4) require that in order to approve research, IRBs determine that informed consent will be sought in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 (including minimization of possible coercion or undue influence). Except for research eligible for expedited review, these findings must be made by the convened IRB, and the convened IRB must receive sufficient information to make these findings. Based on stipulations made by the convened NHLBI IRB at the time of its approval actions, OHRP expressed concerned that on occasion the IRB may be approving research without receiving sufficient information to make all of the determinations required under HHS regulations at 45 CFR 46.111. For example, OHRP noted the following:

> (a) In the April 19, 2005 meeting minutes, the IRB unanimously approved revised protocol 05-H-0088 with eight stipulations, including the following request: "In the memo, on page 2, #6, review compensation in view of short study." Information regarding level of subject compensation appears to be directly relevant to the determination required by HHS regulations at 45 CFR 46.111(a)(4).
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> (b) In the May 3, 2005 meeting minutes, the IRB unanimously approved protocol 05-CC-0154 with ten stipulations, including the following request: "To the protocol and consent document, please add wash out period for cardiac medications and potential risk." Information regarding washout periods for cardiac medications appears to be directly relevant to the determinations required by HHS regulations at 45 CFR 46.111(a)(1) and (2).

Corrective Action: OHRP acknowledges NHLBI's statement that when the convened NHLBI IRB requests substantive modifications or clarifications of protocols or informed consent documents that are directly related to IRB review requirements under 45 CFR 46.111, IRB approval will be deferred pending subsequent review of the requested information/material by the convened IRB.

OHRP finds that the above corrective actions are adequate to address OHRP's findings, and are appropriate under NIH's FWA. As a result, there should be no need for further OHRP involvement. OHRP should be notified if new information that might alter this determination is identified.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Feel free to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Lana Skirboll, OSP, NIH
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