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: 240-453-8297
FAX: 240-453-6909

August 25, 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:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site not-for-cause compliance oversight evaluation of the human subjects protection system for intramural research at the National Heart, Lung, and Blood Institute (NHLBI) July 19-21, 2005. The evaluation involved meetings with senior institutional officials, the chair and several members of the NHLBI institutional review board (IRB), the IRB administrative staff, and investigators who conduct intramural research at NHLBI. In addition, the site visit team examined IRB records for twenty active protocols; the minutes from six meetings of the convened IRB held during March through June 2005; and operating procedures for conducting human subjects research at NHLBI, implemented and developed by NHLBI's Office of Clinical Affairs (OCA) and the National Institutes of Health's Office of Human Subjects Research (OHSR). The OHRP site visit team also observed the NHLBI IRB's convened meeting on July 19, 2005.

Major OHRP Findings

(1) OHRP notes that in general, NHLBI has implemented an excellent system for protecting human research subjects involved in intramural research. In particular, OHRP commends NHLBI for the following:

(a) The NHLBI IRB chairperson and members, and the NHLBI OCA staff, displayed an ongoing commitment to making the protection of human subjects a high priority. The IRB chairperson and OCA staff hold weekly office hours for investigators, thus demonstrating their dedication to helping research investigators comply with the HHS regulations for the protection of human subjects. In addition, OCA conducts an annual full-day retreat for IRB members

to provide a

forum outside of IRB meetings for discussing larger policy, education, or organizational issues.

(b) The NHLBI IRB's review of research proposals at convened meetings is highly substantive and meaningful. Prior to the meetings, each IRB member is expected to review every matter undergoing review at the meeting, including all new protocols and those up for continuing review, all amendments to previously reviewed protocols, and all reported adverse events. The discussion of controverted issues at the July 19, 2005 NHLBI IRB meeting observed by OHRP's site visit team, as well as IRB records and OHRP's interviews with IRB members, demonstrate the IRB's commitment to ensuring satisfaction of the criteria required for IRB approval under Department of Health and Human Services (HHS) regulations at 45 CFR 46.111. For example, the IRB appears to review information routinely regarding (i) subject recruitment and enrollment procedures; (ii) the equitable selection of subjects; (iii) provisions to protect the privacy of subjects and to maintain the confidentiality of data; and (iv) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

(c) The NHLBI IRB appears extremely qualified, due to the experience and expertise of its members, for the scope of research it reviews, in accordance with the requirements of HHS regulations at 45 CFR 46.107(a). OHRP is particularly impressed with the IRB's recruitment of nonscientific members whose appropriately diverse backgrounds facilitate robust discussion of human subject issues at convened meetings.

Additional OHRP Findings and Concerns Regarding Systemic Protections for Human Subjects at NHLBI

Based on its evaluation, OHRP makes the following additional determinations regarding systemic protections for human subjects at NHLBI:

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB chair or another IRB member designated by the chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date on which the IRB chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the NHLBI IRB granted the following extensions of time to conduct continuing review beyond the expiration of IRB approval:

0H00-H-N014 (IRB granted four 60-day extensions in 2002, 2003, 2004, and 2005, respectively; investigator did not request extensions for the 2003, 2004, and 2005 continuing reviews until after IRB approval had expired)

- 01-H-0223 (IRB granted 60-day extension in July 2005)
- 04-H-0268 (IRB granted 30-day extension in July 2005)
- 02-H-0250 (IRB granted 60-day extension in June 2005)
- 85-H-0088 (IRB granted 30-day extension in May 2005)
- 01-CC-0117 (IRB granted 30-day extension in April 2005)
- 04-CC-0194 (IRB granted 60-day extension in March 2005)
- 99-H-0064 (IRB granted 30-day extensions in March 2002 and March 2005)
- 99-H-0037 (IRB granted 30-day extension in February 2004)

OHRP acknowledges that OHSR Information Sheet #9, Section 7, entitled "Request for Extension of Continuing Review Due Date," authorizes convened IRBs to grant extension requests, with or without subject accrual, for up to 90 days beyond the continuing review date. OHRP finds that this extension policy does not satisfy the continuing review requirements of HHS regulations at 45 CFR 46.109(e).

OHRP also finds that the NHLBI IRB conducted continuing review after the expiration date for the following protocols, when extensions of time were neither sought nor granted:

- 01-CC-0231
- 0H00-H-N014
- 99-H-0037
- 00-CC-0165
- 00-H-00003

The IRB and investigators must plan ahead to meet required continuing review dates and must take into account the need for input from scientific committees, expert consultants, or other IRBs. If an investigator fails to provide continuing review information to the IRB, or if the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects must not occur after the expiration of IRB approval.

(3) Under 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 finds 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.

OHRP also has the following additional concern:

(4) [Redacted]

Required and Recommended Actions

Action 1 - Required: By September 12, 2005, please provide OHRP with a satisfactory corrective action plan to address the findings in items (2) and (3) above, and please respond to the concern in item (4) above. Please include in your response a copy of any revised sections of NHLBI and/or OHSR policies or guidance.

Action 2 - Recommended: OHRP recommends that the NHLBI IRB develop a standard approval notice to inform principal investigators, at the time of the initial review and all continuing reviews, of the date on which the IRB approved their protocols. OHRP further recommends that such notices include the date of expiration of IRB approval, and that the notices be maintained in each protocol file.

OHRP appreciates the commitment of NHLBI to the protection of human subjects and is available to assist NHLBI in developing any necessary corrective actions. Please do not hesitate to contact me if you have any questions.

Sincerely,

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

cc: Dr. Lana Skirboll, OSP, NIH
Dr. Alison Wichman, OHSR, NIH
Dr. Joel Moss, NHLBI
Ms. Melissa Bryant, NHLBI
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Karena Cooper, OHRP
Ms. Lynda Lahl, OHRP
Ms. Julia Gorey, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Janet Fant, OHRP
Ms. Patricia El-Hinnawy, OHRP