DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 16, 2001

Peter Bond, Ph.D.
Special Advisor to the Director
Brookhaven Science Associates, LLC
P.O. Box 5000 Building 475D
Upton, NY 11973-5000

RE: Human Research Subject Protections Under Federal Wide Assurance FWA-149

Dear Dr. Bond:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the Brookhaven National Laboratory (BNL) on November 14-15, 2001. The evaluation, conducted by 5 OHRP staff with the assistance of 3 consultants, included meetings with institutional officials, 17 Institutional Review Board (IRB) members, IRB administrative staff, and investigators. The evaluation involved review of IRB files for 20 protocols, and the minutes of more than 18 IRB meetings.

In the course of the OHRP review, the IRB chair, IRB members, and IRB administrative staff displayed an enthusiastic and sincere concern for the protection of human subjects and stated that they view themselves as providing a valuable service to subjects and the research community. OHRP notes that the minutes of the IRB meetings demonstrate substantive and meaningful deliberations for protocols undergoing initial and continuing review. Investigators demonstrated a culture of respect for the IRB process and stated that they appreciated the improvements suggested by the IRB. The IRB administrative staff was helpful and accommodating to OHRP during the site visit.

OHRP Findings

Based upon its review, OHRP makes the following determinations:

(1) OHRP found no evidence to substantiate the allegations referenced in OHRP's October 16, 2001 letter that:

(a) The BNL IRB lacked independence, and the IRB chair, the IRB coordinator, and the Medical Department Chair withheld pertinent human subject protection information from the BNL IRB.

(b) The IRB and investigators failed to ensure that risks to subjects were minimized, as required by HHS regulations at 45 CFR 46.111(a)(1).

(c) Subjects were enrolled in research prior to IRB review and approval of the research, in contravention of HHS regulations at 45 CFR 46.109(a).

(2) OHRP finds that, on occasion, some investigators failed to obtain and document legally effective informed consent of subjects prior to beginning study procedures, as required by HHS regulations at 45 CFR 46.116 and 46.117.

(3) OHRP finds that protocol changes occasionally were implemented prior to IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). In specific, (a) several subjects were entered into protocols even though they did not meet inclusion/exclusion criteria; and (b) additional study procedures were added to some research protocols without IRB approval.

(4) OHRP finds that when reviewing protocol applications, the BNL IRB occasionally appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, some protocols: (a) did not describe all interventions that were to be conducted with research subjects; (b) did not describe the scientific justification for the use of human subjects; and (c) failed to adequately describe inclusion criteria for the protocol.

(5) OHRP finds that informed consent documents reviewed and approved by the BNL IRB occasionally failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(1):

(a) Section 46.116(a)(1): A complete description of the procedures to be followed.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts.

(6) OHRP finds that informed consent documents approved by the BNL IRB frequently included complex language that would not be understandable to all subjects, in contravention of

HHS regulations at 45 CFR 46.116.

BNL Corrective Actions: OHRP acknowledges that in the past 18 months BNL has made substantive changes and improvements to its system for protecting human subjects and has developed, and is implementing, an evolving, detailed Corrective Action Plan. OHRP finds that the following corrective actions adequately address the above findings:

(a) BNL has implemented mandatory education programs regarding human subject protections for investigators and IRB members. Furthermore, BNL encourages and supports attendance of investigators, IRB members and staff at workshops, seminars and courses regarding protection of human subjects.

(b) The BNL IRB is auditing informed consent documents for all research and has made substantial improvements in the completeness and understandability of most informed consent documents.

(c) The BNL IRB and institutional officials have terminated those research protocols evidencing serious and continuing noncompliance.

(d) BNL has hired additional physicians with experience in human subject protections and compliance oversight to oversee and independently audit human subject research activities at the BNL Clinical Research Center (CRC).

(e) The BNL Corrective Action Plan includes a plan for establishing an independent Office of Compliance that will report directly to the FWA authorized institutional official and oversee human subject research activities.

(f) The BNL Corrective Action Plan includes a plan for commissioning an independent review by an external, non-affiliated organization of the BNL Clinical Research Program, including the CRC and the IRB.

(g) BNL has revised its IRB protocol application forms and the Policies and Procedures to help ensure that investigators provide sufficient, detailed information to the IRB for initial review of research.

(h) The IRB membership was expanded to include additional members with experience working with the types of vulnerable subjects enrolled in BNL research.

(i) BNL has implemented appropriate procedures at the CRC for ensuring that only current IRB-approved informed consent documents are used when enrolling subjects in research.

(7) OHRP finds that the BNL IRB Chair occasionally used inappropriate expedited review procedures for review of protocol changes that exceed the limit of "minor changes," in contravention of the requirements of HHS regulations at 45 CFR 46.110(b)(2).
(8) HHS regulations at 45 CFR 46.115(a) require that an institution or IRB shall prepare and maintain adequate documentation of IRB activities. OHRP finds that, in some instances among the IRB files examined by OHRP, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol.

(9) OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the procedures for ensuring prompt reporting to OHRP of any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB, as required by HHS regulations at 45 CFR 46.103(b)(5).

(10) OHRP finds that the minutes of BNL IRB meetings failed to document the vote on all IRB actions including the number of members voting for, against, and abstaining, as required by HHS regulations at 45 CFR 46.115(a)(2). In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(11) OHRP is concerned that the IRB Chair occasionally has used an expedited review procedure to approve protocol amendments for which review by or consultations with a physician member of the IRB would have been appropriate because the amendments may have had medical implications for subjects. OHRP strongly recommends that a physician member of the IRB be involved in these reviews.

(12) OHRP is concerned that some instances of serious noncompliance were not promptly reported to the BNL IRB and OHRP, as required by HHS regulations at 45 CFR 46.103(b)(5).

(13) OHRP is concerned that on occasion the IRB approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research should be deferred, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

Required Action: By January 31, 2002, BNL must submit to OHRP (i) a satisfactory corrective action plan to address findings and concerns stated in paragraphs (7) to (13) above; and (ii) a progress report on the implementation of the BNL Corrective Action Plan referenced above.

At this time, OHRP provides the following additional guidance:

(14) Given the nature of the research overseen by the BNL IRB, OHRP strongly recommends that the composition of the IRB be expanded to include at least one additional physician member. OHRP also recommends that the IRB consult with an expert in pediatrics when reviewing research involving children.

(15) With respect to continuing IRB review of research, OHRP strongly recommends that at least one member of the BNL IRB review the complete IRB protocol file along with the continuing review progress report. The complete IRB file should also be available to other IRB members upon request. Furthermore, OHRP also recommends that the continuing review form solicit information about any complaints by subjects about the research and the reasons for subject withdrawals.

(16) OHRP recommends that: (a) the BNL IRB implement procedures to ensure that all documents in the IRB protocol files are dated; (b) the documentation of expedited review of research be enhanced; (c) correspondence to investigators regarding conditional approval actions more clearly indicate that the investigator may not begin human subject research until written notification is received that all the conditions of approval have been met; and (d) documentation of attendance in the minutes of IRB meetings clearly identify the voting and alternate members.

(17) IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of BNL IRB meetings clearly reflect these determinations regarding risk and approval period (review interval).

(18) The model informed consent document should be modified to include a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, as required by HHS regulations at 45 CFR 46.116(a)(8).

(19) OHRP recommends that BNL adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

OHRP appreciates BNL's commitment to the protection of human subjects. OHRP is available to assist BNL in the development and implementation of these required corrective actions. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Peter Paul, Acting Director, BNL
Dr. Thomas Sheridan, Deputy Director, BNL
Ms. Darcy J. Mallon, IRB Administrator, BNL
Ms. Margaret C. Bogosian, IRB Chair, BNL
Dr. Nora Volkow, BNL
Dr. Julia Yang, BNL
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