DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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April 2, 2003

Jerry S. Flier, M.D.
George C. Reisman Professor of Medicine,
Vice Chair of the Department of Medicine for Research
Beth Israel Deaconess Medical Center
330 Brookline Avenue, Finard 2
Boston, MA 02215

Aram Chobanian, M.D.
Provost
Boston University Medical Campus
715 Albany St.
Boston, MA 02118

RE: Human Research Subject Protections Under Federalwide Assurances FWA-3245 and FWA-301

Research Project: Survey of Two Homeopathic Medicine Practices
BIDMC Project Number: 96-1210-0486
Principal Investigator: David Eisenberg, M.D.

Dear Drs. Flier and Chobanian:

The Office for Human Research Protections (OHRP) has reviewed the Beth Israel Deaconess Medical Center (BIDMC) and Boston University (BU) March 20, 2003 report regarding the above-referenced research project.

Based upon its review of your report, OHRP makes the following determinations regarding the above-referenced research project:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (IRB) review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to

the subjects. OHRP finds that a change to this project was implemented without IRB approval. In specific, the IRB-approved protocol and informed consent document for the project stipulated that nasal swabs and identification of bacteria from those swabs would be performed. The investigator never implemented these procedures; however this protocol change was not reviewed and approved by the IRB.

(2) In accordance with HHS regulations at 45 CFR 46.103(b), an IRB provided for under the BU FWA must review and approve all non-exempt human subject research covered by the BU assurance. OHRP found that the above-referenced research was conducted at BU without review by an IRB designated under the BU FWA.

(3) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show, among other things, actions taken by the IRB and the vote on these actions including the number of members voting for, against, and abstaining. OHRP finds that BIDMC IRB minutes of the meetings at which the above-referenced project was reviewed often failed to meet these requirements. In specific, the actions taken by the IRB for this protocol and the vote on these actions including the number of members voting for, against, and abstaining were not described in the minutes for the December 15, 1997 or the November 16, 1998 BIDMC IRB meetings.

Corrective Actions: OHRP acknowledges that the BIDMC IRB has undergone extensive infrastructure and staffing changes since this research was conducted. These changes include increased staffing to the IRB, increased assistance to investigators in developing protocols, restricting the number of new protocols each board reviews at a meeting, the development of a continuing review IRB, database tracking of protocols, and increased education of investigators. OHRP also acknowledges that the BU investigators will, in the future, submit any research studies involving human subjects to the IRB at BU prior to engaging in human subjects research. OHRP finds that these corrective actions adequately address the above findings and are appropriate under the BU and BIDMC FWAs.

(4) OHRP's February 13, 2003 letter to BIDMC and BU presented allegations that the above-referenced research project failed to ensure that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, as required by HHS regulations at 45 CFR 46.111(a)(1) and (2). OHRP acknowledges that the research was not a treatment study but an observational study of those children whose parents had elected to pursue homeopathic care before the study was initiated and that the risks to children were no more than a minor increase over minimal risk. Therefore, OHRP finds that this allegation was not substantiated.

(5) OHRP's February 13, 2003 letter to BIDMC and BU presented allegations that the informed consent document for the above-referenced research project failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

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

(b) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research.

(c) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(d) Section 46.116(a)(6): For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

OHRP finds that these allegations were not substantiated.

(6) OHRP's February 13, 2003 letter to BIDMC and BU presented allegations that the above-referenced research project involved children; the risk of the research was more than a minor increase over minimal risk; the research had no prospect of direct benefit to the subject; the intervention was not likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and therefore was not approvable under HHS regulations at 45 CFR 46.406.

OHRP finds that this allegation were not substantiated. However, OHRP reminds BIDMC that HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP strongly recommends that where HHS regulations require specific findings on the part of the IRB, such as approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings.

(7) OHRP's February 13, 2003 letter to BIDMC and BU presented allegations that the above-referenced research project involved subjects who were vulnerable to coercion and undue influence but that additional safeguards were not included in the study to protect the rights and welfare of these subjects, in contravention of HHS regulations at 45 CFR 46.111(b). OHRP finds that this allegation could not be substantiated.

As a result of these determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

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,

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

cc with enclosures:
Dr. Alan Lisbon, Chair, BIDMC IRBs
Dr. Anna Johansson, HSA, BIDMC
Dr. David Eisenberg, BIDMC
Dr. Jonathan Woodson, IRB Chair IRB#1, BUMC
Dr. Louis Vachon, IRB Chair IRB#2, BUMC
Dr. Richard Saitz, IRB Chair IRB#3, BUMC
Ms. Helen M. Lawless, BUMC
Dr. Elizabeth Barnett, BUMC
Dr. Jerome Klein, BUMC
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