DEPARTMENT OF HEALTH & HUMAN SERVICES

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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1073

Dear Mr. Allen and Mr. O'Hara:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site not-for-cause evaluation of the human subject protection system at the State University of New York/Downstate Medical Center and Research Foundation (SUNY Downstate) on April 15-16, 2002. The evaluation, conducted by 3 OHRP staff with the assistance of 2 consultants, involved meetings with senior institutional officials; the Chair, Vice-Chair and 17 members of the SUNY Downstate Institutional Review Boards (IRBs); the IRB administrative staff; and several investigators who conduct human subject research supported by the Department of Health and Human Services (HHS). The evaluation involved review of IRB files for more than 30 protocols, 12 exempt activities, and the minutes of IRB

meetings convened over the past 2 years.

OHRP Findings Regarding Systemic Protections for Human Subjects at SUNY Downstate

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

(1) OHRP finds that overall SUNY Downstate has implemented an adequate system for protecting human research subjects. Of note, OHRP commends SUNY Downstate for the following:

(a) Senior SUNY Downstate officials displayed a sincere commitment to the protection of human subjects.

(b) The SUNY Downstate IRB Chair, members, and administrative staff displayed a sincere concern for the protection of human research subjects and appeared to be highly dedicated.

(c) The minutes of the SUNY Downstate IRB meetings meet the requirements of HHS regulations at 45 CFR 46.115(a)(2).

(d) In general, the SUNY Downstate IRBs appear to be sufficiently qualified through the experience and expertise of its members, and the diversity of its members, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required by HHS regulations at 45 CFR 46.107(a).

(e) The SUNY Downstate IRB records were complete, well-organized, and satisfied the requirements of HHS regulations at 45 CFR 46.115.

(f) The IRB-approved informed consent documents for active SUNY Downstate human subject research protocols that were reviewed by OHRP were generally in compliance with the requirements of HHS regulations at 45 CFR 46.116, except in limited circumstances as noted below.

(2) HHS regulations at 45 CFR 46.111(b) require that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons, the IRB must ensure that additional safeguards have been included in the study to protect the rights and welfare of these subjects. Based upon its review of IRB records and discussions with the IRB members and Chair, OHRP finds (a) that SUNY Downstate investigators frequently involve subjects who

are likely to be vulnerable to coercion or undue influence for a variety of reasons; and (b) little evidence that the SUNY Downstate IRBs consistently ensure that additional safeguards are included in studies involving such subjects.

Options for additional safeguards that could be considered include, but are not limited to the following: (a) independent consent monitors; (b) use of instruments to assess subject comprehension prior to proceeding with research interventions and interactions; (c) implementation of research subject advocates or an ombudsman; and (d) implementation of independent assessment of capacity to consent for potential subjects who may have impaired capacity to consent.

Furthermore, HHS regulations at 45 CFR 46.109(e) stipulate that IRBs have the authority to observe or have a third party observe the consent process and the research. OHRP encourages IRBs to use this authority.

(3) OHRP finds that for some protocol applications, the IRB failed to obtain sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, some protocol applications were very abbreviated and lacked important information regarding (a) scientific background and study design; (b) subject recruitment and enrollment procedures; (c) the equitable selection of subjects; (d) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (e) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable (e.g., see protocol numbers 99-139, 01-015, 01-156, 02-035, and 02-046).

(4) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of IRB documents appears to indicate that the SUNY Downstate IRBs fail to make the required findings on a consistent basis when reviewing research involving children.

(5) The HHS regulations require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (see 45 CFR 46.116 and 46.117). Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language understandable to them.

OHRP is concerned that the SUNY Downstate IRBs do not routinely require informed consent documents in the native language of likely potential subjects who do not speak English. Furthermore, OHRP is concerned that the IRBs on occasion approve protocols for which the investigator has stipulated that individuals who do not speak English will be excluded without

providing a justification for such an exclusion criterion.

(6) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364--60367. OHRP is concerned that on occasion the SUNY Downstate IRBs inappropriately applied expedited review to research that involved greater than minimal risk (e.g., see protocol numbers 00-049, 01-173, and 02-024)

(7) HHS regulations at 45 CFR 46.116(a)(1) require that informed consent include, among other things, a description of all procedures to be followed. OHRP finds that this requirement was not satisfied for the IRB-approved informed consent document for protocol number 97-173 (i.e., study washout period was not described).

(8) HHS regulations at 45 CFR 46.116(a)(4) require that informed consent include a disclosure of appropriate alternative procedure or courses of treatment, if any, that might be advantageous to the subject. OHRP finds that this requirement was not satisfied for the IRB-approved informed consent document for protocol number 99-152.

(9) HHS regulations at 45 CFR 46.116(a)(8) require that informed consent include a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. OHRP finds that this requirement was not satisfied for the IRB-approved informed consent document for protocol number 01-156.

(10) HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide meeting space and sufficient staff to support the IRB's review and recordkeeping duties. OHRP is concerned that the IRB administrative staff lacks (a) sufficient clerical staff to support the IRB's recordkeeping duties; and (b) adequate private office space to conduct sensitive IRB duties.

(11) With respect to the determination of whether specific research protocols are exempt under HHS regulations at 45 CFR 46.101(b), OHRP noted the following:

> (a) The IRB Chair on occasion appears to confuse the concepts of research not involving human subjects as defined by HHS regulations at 45 CFR 46.102(f) and human subject research that is exempt under 45 CFR 46.101(b).
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> (b) There was a discrepancy for protocol number 02-003 where the project was determined to be exempt under 45 CFR 46.101(b)(2) because the research questionnaire was considered anonymous, but the questionnaire in the IRB file included information that would clearly identify the family.

Required Action: By May 24, 2002 please provide OHRP was a satisfactory corrective action plan to address the above findings and concerns.

OHRP provides the following additional guidance:

(12) As previously noted, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. In order to satisfy these requirements for research protocols involving survey instruments or questionnaires, the IRB should receive and review, among other things, copies of all proposed survey instruments and questionnaires.

(13) In order to ensure substantive and meaningful continuing IRB review of research, primary reviewers should receive a copy of the complete protocol including any modifications previously approved by the IRB (see OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm).

(14) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

(15) Regarding the SUNY Downstate's written IRB procedures, OHRP recommends the following:

(a) The procedures should be expanded to include a description of the procedures which the IRBs will follow for reporting their findings and actions to the institution.

(b) The definition of "minimal risk" should be revised to match the definition as stated in HHS regulations at 45 CFR 46.102(i).

(c) The section on "Emergency Use" should be revised to avoid any confusion about whether human subject research may be conducted at SUNY Downstate without prior IRB review and approval.

HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval (see 45 CFR 46.103(b) and 46.116(f) and OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc91-01.htm). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

OHRP appreciates SUNY Downstate's continued commitment to the protection of human subjects. Please feel free to contact me if you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Eli Friedman, IRB Chair, Boards A, B and E, Downstate
Dr. Enzo Bard, IRB Administrator, Downstate
Ms. Ruth Browne, Executive Director, Arthur Ashe Institute
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