DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 5, 2004

Roberta Luskin-Hawk, M.D.
President
AIDS Research Alliance-Chicago
2800 North Sheridan Road, Suite 108
Chicago, Illinois 60657

Mathias D. Maguire
Interim Chief Executive Officer
Catholic Health Partners
2520 North Lakeview Avenue
Chicago, Illinois 60614

RE: Human Research Subject Protections Under Cooperative Project Assurances (CPA) T-4522 and T-4815 and Federalwide Assurance (FWA) 1320

Research Project: A Randomized, Open-Label Study of the Impact of Two Doses of Subcutaneous Recombinant IL-2 (Proleukin) on Viral Burden and CD4+ Cell Count in Patients with HIV-1 Infection and CD4+ Cell Counts $ 300/mm^3
Principal Investigator: Roberta Luskin-Hawk, M.D.
Project Number: CPCRA 059
HHS Award Number: 2U01 AI42199-09

Dear Dr. Luskin-Hawk and Mr. Maguire:

The Office for Human Research Protections (OHRP) has reviewed the AIDS Research Alliance-

Chicago (ARAC) and Catholic Health Partners (CHP) June 14, 2002 joint report that was submitted in response to OHRP's April 8, 2002 letter to ARAC and CHP regarding allegations of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research. OHRP has also reviewed ARAC's July 30, 2002 letter which was submitted to the Food and Drug Administration (FDA) in response to the inspectional observations listed in the Form FDA 483 issued to Dr. Luskin-Hawk on May 5, 2002. OHRP apologizes for the delay in its response.

Based upon its review of ARAC's and CHP's June 14, 2002 joint report, as well as additional documentation requested by OHRP regarding the FDA clinical investigator inspection of the above-referenced study project submitted by ARAC on September 26, 2003, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds that version 2.0 of the informed-consent document reviewed and approved by the CHP Institutional Review Board (IRB) on behalf of ARAC failed to adequately address the reasonably foreseeable risks and discomforts of the research, as required by HHS regulations at 45 CFR 46.116(a)(2). In specific, OHRP finds that the previously undisclosed foreseeable risks and discomforts associated with the subcutaneous administration of IL-2, as described in the January 29, 1999 Investigator Brochure (IB), were not clearly identified within the context of the foreseeable risks and discomforts associated with the intravenous administration of IL-2 in version 2.0 of the informed- consent document. Accordingly, OHRP finds that ARAC failed to amend version 2.0 of the informed-consent document to include an updated description of the foreseeable risks and discomforts associated with the subcutaneous administration of IL-2 described in the IB, as required by HHS regulations at 45 CFR 46.116(a)(2).

(2) In its April 8, 2002 letter, OHRP presented the allegation that the informed-consent documents reviewed and approved by the CHP IRB failed to comply with certain requirements of HHS regulations at 45 CFR 46.116. In specific, it was alleged that:

(a) The IRB-approved informed-consent document, version 2.0, included exculpatory language.

(b) The informed-consent documents, version 1.0 and 2.0, failed to describe the likelihood of and increase in the subject's HIV viral load.

(c) The informed-consent documents, version 1.0 and 2.0, failed to inform the subjects

of additional costs to the subjects that resulted from participation in the research.

OHRP finds that these allegations could not be substantiated.

(3) OHRP finds that the CHP IRB lacked sufficient information to make the determinations required for approval of the above-referenced research under HHS regulations at 45 CFR 46.111. In specific, OHRP finds that the CHP IRB failed to receive and review the IB before approving the above-referenced research. The IB provided a detailed list of adverse events associated with subcutaneous administration of IL-2. These adverse events were not described as risks associated with receiving IL-2 subcutaneously in version 2.0 of the IRB-approved informed-consent document, as previously described in item (1) above.

Action 1 - Required: By May 14, 2004, ARAC must submit to OHRP a detailed corrective- action plan to address the above findings.

(4) In its April 8, 2002 letter, OHRP presented the allegation that the investigators conducting the research failed to assure that risks to subjects were minimized, as required by HHS regulations at 45 CFR 46.111(a)(1). In specific, it was alleged that the investigators failed to monitor subjects for study-agent toxicities and reduce study-agent dosage to manage toxicities.

OHRP finds that this allegation could not be substantiated.

(5) In its April 8, 2002 letter, OHRP presented the allegation that the investigators failed to adequately monitor and supervise the research nurses involved in the day-to-day conduct of the study.

ARAC's and CHP's June 14, 2002 joint report stated the following:

> "A recent FDA audit of a subset of patients in CPCRA 059 at ARAC sites revealed insufficient physician oversight of research nurse activities. In response to the audit findings, Roberta Luskin-Hawk, ARAC Principal Investigator, convened mandatory investigator conference call (*sic*) on April 16 and 17, 2002 to discuss investigator roles and responsibilities. Two investigators who were unable to attend were contacted personally.
>
> "In order to enhance the physician subinvestigators' ability to oversee conduct of the

> trial the ARAC staff will provide study specific time and event tables and patient study visit schedules to be placed in patient's medical records, whenever possible."

OHRP finds that ARAC acknowledged and confirmed FDA's May 5, 2002 inspectional observations regarding investigator failure to monitor certain subjects, and to monitor and supervise certain research nurses involved in the day-to-day conduct of the study for the above-referenced study project.

Corrective Action: OHRP acknowledges ARAC's corrective actions to FDA's inspectional observations. OHRP finds that these corrective actions adequately address the above determinations and are appropriate under the ARAC FWA.

(6) In its April 8, 2002 letter, OHRP presented the allegation that the investigators deviated from the IRB-approved protocol, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4). In specific, it was alleged that some subjects were prescribed corticosteroids, an intervention not permitted under the IRB-approved protocol.
In response to this allegation, ARAC's and CHP's June 14, 2002 joint report stated the following:

> "The protocol did not state that administration of corticosteroids to study subjects was dangerous, contraindicated or prohibited but merely that they should be 'avoided.'"

As a result, OHRP finds that this allegation was not substantiated.

(7) In its April 8, 2002 letter, OHRP presented the allegation that the investigators failed to accurately record and report increases in HIV viral-load measurements for some subjects. In response to this allegation, ARAC's and CHP's June 14, 2002 joint report stated the following:

> "ARAC became aware during the conduct of CPCRA 059 of a research nurse whose job performance was substandard. There was evidence that she had not forwarded laboratory results to the sub-investigators on a regular basis. The ARAC principal investigator, project coordinator and key research staff responded immediately and reviewed all data from that site. A detailed review of her work and discussions with her suggested that [she] had been trying to hide her deficiencies. The research nurse was asked to resign and she complied....

> "The issue was reviewed by Dr. Luskin-Hawk with all ARAC physician sub-investigators, with special emphasis on investigator responsibilities. A standardized tracking mechanism for laboratory results was developed. All lab reports are reviewed in the central ARAC office for serious toxicities by the project coordinator or research nurse on a daily basis (Monday through Friday). All labs are signed, dated and faxed to the patient's research site. If the project coordinator or RN identifies a grade IV toxicity, the research nurse is called immediately and told to notify the investigator. The research nurse routinely forwards the laboratory report to the physician investigator for review and signature, prior to filling. The project coordinator is responsible for oversight of this process."

OHRP finds that ARAC acknowledged and confirmed FDA's inspectional observation regarding investigator failure to accurately record and report increases in HIV viral-load measurements for certain subjects.

Corrective Action: OHRP acknowledges ARAC's corrective actions described above. OHRP finds that these corrective actions adequately address the above determinations and are appropriate under the ARAC FWA.

(8) In its April 8, 2002 letter, OHRP presented the allegation that the investigators failed to promptly report serious adverse events in accordance with the IRB-approved protocol. ARAC's and CHP's June 14, 2002 joint report stated the following:

> "In accordance with CPCRA procedures, research personnel were instructed to report Serious Adverse Events within 3 days and grade IV adverse events within 30 days. Compliance with this standard was monitored by the CPCRA Clinical Site Monitoring Group and the CPCRA Management Group. To the best of our knowledge every protocol defined SAE and grade IV adverse events were reported in a timely manner."

As a result, OHRP finds that the above allegation was not substantiated.

(9) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the 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 the investigator changed the exclusion criteria for subject selection for one subject, absent IRB review and approval. In specific,

OHRP notes the following:

(a) Item (4) of the exclusion criteria for patient selection in version 1.0 and 2.0 of the above-referenced research project stated the following:

> "Use of systemic corticosteroids, immunosuppressants, or experimental cytotoxic agents (including hydroxyurea) **within 4 weeks prior to study randomization** [emphasis added]."

(b) Item 7.b. in ARAC's July 30, 2002 letter to FDA stated the following:

> "**A medical record documents that the patient was prescribed prednisone tablets on 1/19/99. The patient was randomized on 2/22/99. A protocol exclusion criterion was the use of systemic corticosteroids within 4 weeks prior to study randomization. There is no documentation of the date the patient stopped treatment with prednisone** [emphasis in original].
>
> "After discussion with the investigator, it was verified this short course of steroids had been completed prior to randomization, however it is likely that they were taken within the exclusionary period. **We recognize that this is a randomization violation** [emphasis added]...."

Corrective Action: OHRP acknowledges that the ARAC has developed a randomization form to screen for any deviations from inclusion/exclusion criteria. Future ARAC randomization forms will be reviewed by the Primary Investigator and the Project Coordinator in order to ensure sufficient detail and clarity. OHRP finds that these corrective actions adequately address the above determinations and are appropriate under the ARAC FWA.

OHRP makes the following additional findings regarding ARAC's and CHP's system for the protection of human subjects:

(10) HHS regulations at 45 CFR 46.115(a)(2) require, in part, that minutes of IRB meetings be in sufficient detail to show attendance at the meeting; actions taken by the IRB; and the vote on these actions, including the number of members voting for, against, and abstaining. OHRP finds that the minutes of IRB meetings often failed to satisfy these requirements. Furthermore, OHRP finds that the minutes often did not document separate deliberations, actions, and votes for each

individual protocol undergoing continuing review.

(11) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited-review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area.

(a) OHRP finds that at the April 14, 2000 and July 14, 2000 IRB meetings, proxy votes were solicited by the IRB chair from IRB members who could not attend all or part of the IRB meetings. OHRP emphasizes that proxy votes may not be counted as votes to approve or disapprove research at convened meetings, or counted for purposes of establishing a quorum.

(b) OHRP finds that the IRB failed to meet the quorum requirements at the June 9, 2000 IRB meeting and for part of the July 14, 2000 IRB meeting. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored.

(12) HHS regulations at 45 CFR 46.107(a) require that the IRB have members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. OHRP finds that the IRB minutes for July 14, 2000, August 11, 2000, and September 8, 2000 record the informal designation of alternates for regular voting members. OHRP notes that an alternate member(s) may be designated, as needed, for a regular voting member(s). However, these alternates should be formally appointed and identified on the IRB roster. The appointment of an alternate member(s) should be based on expertise corresponding to that of the regular voting member(s).

(13) HHS regulations at 45 CFR 46.103(a), 46.103(b)(5), and 46.108(a) require, in part, that any serious or continuing noncompliance with regulations relating to the protection of human subjects be promptly reported to appropriate institutional officials, appropriate federal department or agency heads, and OHRP. OHRP notes the following FDA correspondence with CHP:

(a) A December 9, 2002 FDA Warning Letter to Matthias McGuire, Acting CEO, CHP that imposed the following regulatory sanction on the CHP IRB in accordance with FDA regulations at 21 CFR 56.120(b)(2):

> "**No new subjects** [emphasis in original] are to be admitted to ongoing studies that are subject to 21 CFR Parts 50 and 56 until you have received notification from this office that adequate corrections have been made."

(b) An April 11, 2003 FDA Warning Letter to Kathleen K. DeVine, CEO, CHP that imposed the following additional regulatory sanction on the CHP IRB in accordance with 21 CFR 56.120(b)(2), based on the lack of an adequate response and appropriate corrective actions to the deficiencies cited in FDA's December 9, 2002 FDA Warning Letter:

> "...no new studies that are subject to Parts 50 and 56 of the FDA regulations are to be approved by your IRB. This, [*sic*] restriction will remain in effect until you are notified in writing by FDA that the IRB's corrective actions are satisfactory, that the IRB meets the requirements of Part 56, and that the restrictions have been removed."

OHRP notes that these violations of FDA regulations also represent serious or continuing noncompliance, which HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require to be promptly reported to OHRP. OHRP finds no evidence in OHRP reporting files that ARAC or CHP ever reported to OHRP these violations or the FDA regulatory sanctions taken in response to these violations.

Action 2 - Required: By May 14, 2004, ARAC must submit to OHRP a detailed corrective- action plan to address the above findings (10) - (13). The corrective-action plan should include revised IRB policies and procedures addressing each of the issues raised in findings (10) - (13), and copies of correspondence which document satisfactory corrective actions which have been made by the CHP IRB to the FDA regulatory sanctions stated in finding (13)(a) and (b) above.

OHRP has the following additional concern:

(14) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the

initial or continuing review of any project in which the member has a conflicting interest. Roberta Luskin-Hawk, M.D., President and Principal Investigator, ARAC, appears to serve as a voting member of the CHP IRB. OHRP suggests that the duties of Dr. Luskin-Hawk as the president and principal investigator of a clinical-trials program are likely to create a real or apparent conflicting interest, and that this individual ordinarily should not serve as a *voting* IRB member. **Please respond.**

OHRP has the following guidance regarding CHP IRB's written policies and procedures dated May 7, 2002 (Procedures):

(15) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. The definition of quorum under Article II-Section 3 of the Procedures states:

> "**Quorum** [emphasis in original]. A majority of the members will constitute the quorum for the transaction of business at any meeting of the IRB."
>
> OHRP recommends that this section be revised to indicate that at least one nonscientist member must be present.

(16) Under the Expedited Review Application form attachment to the Procedures, please note that the list of categories of research that may be reviewed by an IRB through expedited procedures was updated by OPRR and FDA in the Federal Register on November 9, 1998 (63 FR 60364). The list is available on the OHRP web site at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm.

Please provide your response to the above findings and concerns to OHRP no later that May 14, 2004. Please do not hesitate to contact me should you have any questions.

Sincerely,

Robert J. Meyer

Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Robert J. O'Mara, IRB Chairperson, CHP
Mr. John Fraham, CHP
Mr. Edward M. Goodwin, ARAC
Commissioner, FDA
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