DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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February 13, 2007

Elizabeth R. Carver, J.D.
Vice President & General Counsel
HCA-HEALTHONE LLC
4900 South Monaco Street
Suite 380
Denver, CO 80237

Milt Bollman
CFO
HealthOne
600 South Cherry St., Suite # 217
Denver, CO 80246

RE: Human Research Subject Protections Under Federalwide Assurances FWA- 2864 and 2839

Research Project: Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (The 'SUN' Study)
Principal Investigator: John Hammer, M.D.
Project Number: CDC protocol ID 3979

Dear Ms. Carver and Mr. Bollman:

The Office for Human Research Protections (OHRP) has reviewed the letter written by attorney Michael Schmidt dated April 18, 2006 as well as the accompanying materials that were submitted in response to OHRP's March 31, 2006 letter to HCA-HealthOne LLC and HealthOne, regarding allegations of 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.

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

(1) 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 the investigator's failure to inform the subject complainant of positive test results for Hepatitis C virus during his participation in the SUN study constitutes a protocol change that was implemented without IRB review and approval.

OHRP notes that following the IRB's Feb. 27, 2006 decision to suspend accrual of new subjects pending an IRB inquiry into the subject's complaint, the investigator's response to the IRB inquiry includes the following statement contained in the Incident Report submitted to the Center for Disease Control (CDC) in either February or early March 2006:

> It is the responsibility of the principal investigator to make sure the results of study-related tests are given to the enrollees' primary care physicians as soon as they are available and to highlight any abnormal results. It is the responsibility of the enrollees' primary care physician to communicate these results to the enrollee, unless the results indicate a potentially life-threatening condition or a condition otherwise requiring immediate treatment, in which case the principal investigator is to contact the enrollee as quickly as possible, which may require a direct contact.

OHRP notes that the March 15, 2006 letter from the IRB chairperson to the investigator states the following regarding the IRB deliberation at the March 15, 2006 meeting:

> It was the vote of the Board that this study remains closed to accrual. It is clearly stated in the consent form on page #9, "What will happen if you find a health problem during the study?", that the onus is on the Investigator to take every means necessary to notify the patient about the findings. These steps were not followed. Even though the practice had two findings of Hepatitis C, this patient was not notified.

The IRB determined that the study would remain closed to accrual until the investigator created certain written procedures and responded to IRB questions. The investigator was required to develop standard operating procedures for his medical practice related to delineating research study visits from office visits for standard of care and to notification and follow-up regarding test result.

During the full board meeting on April 19, 2006, the IRB discussed the investigator's April 3, 2006 response that "outlined the changes made at his practice for improvements in patient contact methodologies and staff cross-checks." The IRB voted to rescind the suspension of new accrual.

Corrective Actions: OHRP has reviewed the investigator's April 3, 2006 response and finds that the IRB's actions regarding this noncompliance were satisfactory. However, in its March 31, 2006 letter, OHRP also required that the following item be included in the

institution's response: "If your investigation reveals noncompliance, a description of any corrective actions that have been or will be taken by your institution to prevent such noncompliance from recurring."

OHRP notes that the institution's response focused on this particular incident. However, OHRP encourages HCA-HealthOne LLC to develop standard operating procedures that addresses the manner in which your institution will strive to prevent other investigators at your institution from implementing changes to IRB-approved protocols without prior review and approval by the IRB.

OHRP notes that the response to the following required item, "A description of your institution's program for ensuring that all IRB members, all IRB staff and all research investigators are appropriately educated, on an ongoing basis, about the ethical principles and regulatory requirements for the protection of human subjects," was a reference to a paragraph in the HealthOne Alliance IRB Policy and Procedures Manual. The section entitled "Orientation and Education" in the manual contains the following paragraph:

> Each member of the IRB, at a minimum, will receive an orientation folder which includes the Policy and Procedures Manual and Appendices. In addition, members may, from time to time, be provided an opportunity to attend educational seminars or workshops related to investigational research and the role of the IRB.

OHRP notes that absent in the institution's response is any reference to ongoing education and training for IRB staff and research investigators. OHRP recommends that such ongoing training be provided.

(2) It was alleged that the investigator of the above-referenced study failed to provide a copy of the informed consent document to the subject, as required by HHS regulations at 45 CFR 46.117(a). OHRP is unable to substantiate this allegation.

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,

Karena Cooper, J.D., M.S.W.
Division of Compliance Oversight

cc: Judy Hatch, IRB Administrator, HCA-HealthOne LLC
Dr. Robert M. Rifkin, IRB Chairperson, HCA-HealthOne LLC
Dr. Fred W. Hetzel, Vice President, HealthOne
Michael Schmidt, Attorney
Deborah Holtzman, CDC
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
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Ms. Carla Brown, OHRP