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March 15, 2011

Robert B. Wellman, M.D.
Chief Executive Officer Carle Physician Group
Carle Foundation
602 West University Avenue
Urbana, IL 61801

RE: Human Research Protections Under Federalwide Assurance FWA-2292

Research Project: A Clinical Trial of Adjuvant Therapy Comparing Six Cycles of 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) to Four Cycles of Adriamycin and Cyclophosphamide (AC), with or without Celecoxib, in Patients with Node-Negative Breast Cancer

HHS Protocol Number: NSABP-B-36

Research Project: Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer

HHS Protocol Number: CALGB 80405

Research Project: Valerian for Improving Sleep in Patients With Cancer Receiving Adjuvant Therapy

HHS Protocol Number: NCCTG N01C5

Research Project: A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin Versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

HHS Protocol Number: ECOG E52

Research Project: Phase II Trial of Docetaxel and Carboplatin Administered Every Two Weeks as Induction Therapy for Stage II or Stage III Breast Cancer

HHS Protocol Number: NCCTG N0338

Research Project: A Phase II Study of Epratuzumab, Rituximab (ER)-CHOP for Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

HHS Protocol Number: NCCTG N0489

Research Project: Phase III Trial comparing Adjuvant Temozolomide with Dose-Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma

HHS Protocol Number: RTOG 0525

Research Project: A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin and Cetuximab (C225) [Followed by Surgery for Selected Patients] For Stage III and IV Head and Neck Carcinomas

HHS Protocol Number: RTOG 0522

Research Project: A Phase III Trial of Continuous Schedule AC + G Vs. Q2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer

HHS Protocol Number: SWOG S0221

Research Project: Cyclophosphamide and Doxorubicin (CA X 4 Cycles) Versus Paclitaxel (4 Cycles) As Adjuvant Therapy for Breast Cancer in Women with 0-3 Positive Axillary Lymph Nodes: A Phase III Randomized Study

HHS Protocol Number: CALGB 40101

Research Project: A Phase II Study of CCI-779 in Combination with Rituximab in Patients with Relapsed or Refractory Mantle Cell Lymphoma

HHS Protocol Number: NCCTG N038H

Principal Investigator: Dr. Kendrith M. Rowland, Jr.

Dear Dr. Wellman:

Thank you for the Carle Foundation Hospital emails dated December 15, 2009 (quarterly report), January 13, 2010 (vulnerable population audit), February 26, 2010 (follow-up report regarding vulnerable population audit), March 15, 2010 (quarterly report), April 15, 2010 (lapsed studies audit), June 15, 2010 (quarterly report and expedited review audit), September 27, 2010 (quarterly report and IRB procedures audit) and February 4, 2011 (Carle Foundation Policies and Procedures) in response to our September 21, 2009 and December 16, 2009 letters. In addition, thank you for the January 4, 2010 Carle Clinic Association letter.

Please note that prior to October 15, 2010 the Carle Foundation Hospital and Carle Clinic Association operated as two separate Federalwide Assurance (FWA) -holding institutions; Carle Foundation Hospital holding FWA-2292, and the Carle Clinic Association holding FWA-5173. On October 15, 2010, as the result of an April 1, 2010 merger of the two institutions, the Carle

Clinic Association deactivated its FWA and all Carle Clinic Association research activities became covered under the Carle Foundation FWA-2292. Given that this merger occurred during our investigation of these two separate FWA-holding institutions, we will now address these previously separate FWA-holding institutions as the newly combined research entity Carle Foundation.

Based on the information submitted, we make the following determinations regarding Carle Foundation:

A. Assessment of Corrective Actions to Address OHRP’s Prior Determinations Regarding the Above-Referenced Research:

In our December 16, 2009 letter, we required the Carle Clinic Association to provide our office with clarification regarding Section 2(A)(i) of a draft IRB Authorization Agreement (IAA) to be executed by the Carle Clinic and an external IRB. In specific, we asked for clarification regarding what will happen to information relating to local context issues that is gathered by Carle Clinic personnel.

In a letter dated January 4, 2010, the Carle Clinic Association explained that each new study is evaluated for feasibility and local context before being submitted to the external IRB of record. Each study is reviewed by multiple Carle Clinic Association departments and staff members for operational feasibility and by a patient advocate for local context issues. Any information gathered by the Carle Clinic regarding local context issues is shared with the external IRB. Of note, the external IRB submission form for both initial review and continuing review includes a place for the institution to submit comments regarding local context: any comments provided by the patient advocate is reported to the external IRB on this form.

In an email dated February 9, 2011, the Carle Foundation verified that the process described above is being followed for all federally-funded studies being conducted at the Carle Foundation Cancer Center. We understand from the email that different local research context process is being followed for federally-funded studies being conducted by Carle Foundation, but outside of the Cancer Center. For such studies, the IRB relies upon the Carle Foundation Scientific Research Committee (SRC) to assess studies for feasibility, appropriateness, and assessment of local context issues. In regard to local research context issues, the SRC is charged with communicating any concerns or issues regarding local context to the reviewing IRB.

We determine that this explanation adequately addresses our concern and is appropriate under the Carle Foundation FWA.

B. Assessment of Corrective Actions to Address OHRP’s Prior Determinations Regarding the Carle Foundation Hospital and Carle Clinic Human Subjects Protection Programs:

- (1) We previously determined that the Carle Foundation Hospital Signatory Official and a prior Carle Clinic Signatory Official failed to fulfill the obligations imposed by Department of Health and Human Services (HHS) regulations for the protection of human subjects and the institutions' FWAs as required by HHS regulations at 45 CFR 46.103(c). We identified specific corrective actions to be taken, and asked the Carle Foundation Hospital to provide our office with quarterly reports regarding: (a) implementation of the corrective actions identified in our September 21, 2009 letter; and (b) the proposed merged organization's future plans for the protection of human subjects.

Carle Foundation Corrective Action: To date, the Carle Foundation has:

- (a) Implemented all corrective actions identified in our September 21, 2009 and December 19, 2009 letters;
- (b) Completed all requested subject specific audit reports; and
- (c) Provided our office with continuous updates regarding the integration of Carle Clinic Association and Carle Foundation Hospital. As stated above, the Carle Clinic ceased to function as a research institution as of October 15, 2010. As of that date, the Carle Clinic Association and Carle Foundation Hospital began operating as Carle Foundation under FWA 2292, a merged organization with one Institutional Official and a unified research compliance program.

We determine that the implementation of all of the corrective actions noted above adequately addresses our determinations and are appropriate under the Carle Foundation FWA.

- (2) In our September 21, 2009 letter, the Carle Foundation Hospital was asked to clarify whether and how the Carle IRB considers the requirements of subpart B of the HHS protection of human subjects regulations when reviewing research involving pregnant women, fetuses or neonates. We asked this question after reviewing study 080431 "One Kids, Illinois Kids Development Study," which involved the recruiting of pregnant women for interviews, urine collection, and follow-up of newborns and noting that there was no reference to the Carle IRB making the determinations required under subpart B for this research. When responding to this question, the Carle Foundation Hospital limited its response to the study referenced above although the original request was for Carle Foundation Hospital to clarify whether and how the Carle IRB considers the requirements of subpart B when reviewing all research involving pregnant women, fetuses or neonates. As a result of this oversight, in our December 16, 2009 letter we asked the Carle Foundation Hospital to audit all currently active research involving pregnant women, fetuses or neonates to determine whether the Carle IRB made the required findings under subpart B.

The Carle Foundation Hospital conducted an audit of all currently active research involving pregnant women, fetuses or neonates (a total of four studies) to determine whether the Carle IRB made the required findings under subpart B. The audit revealed, and we determine, that the Carle IRB failed to make the required findings under subpart

B when reviewing the four research protocols involving pregnant women, fetuses or neonates.

Carle Foundation Corrective Action: As a result of this audit, the Carle IRB

- (a) Re-reviewed and approved all four studies after making the required findings under subpart B;
- (b) Revised its reviewer worksheet to incorporate a “Required Reviewers Comments” section so that reviewers are reminded of and can appropriately document/acknowledge the requirements for review under subpart B.

We determine that the corrective actions noted above adequately address our determination and are appropriate under the Carle Foundation FWA.

C. Recommendations Regarding Carle Foundation IRB Policies and Procedures

- (1) Carle Foundation Policy 402. Item 4 under the section “Criteria of IRB Approval” outlines the criteria that will be used by the IRB to determine whether third party verification of information submitted by an investigator is required. We note that while this section of the policy refers to Carle Foundation Policy 408 entitled “Verification from Sources Other Than the Principal Investigator That No Material Changes Have Occurred to IRB-Approved Research,” the criteria listed in Carle Policy 402 are different from the criteria listed in Carle Policy 408, as well as Carle Research Policy 121 entitled “Verification from Sources other than the Principal Investigator that no Material Changes have Occurred to IRB-Approved Research.” We recommend that you correct this inconsistency.
- (2) Carle Foundation Policy 403. We note that this policy delineates the procedures to be followed when an investigator plans a proposed change to research and the proposed change either (i) is not necessary to eliminate apparent immediate hazards to the subjects (must seek prior IRB review and approval); or (ii) is necessary to eliminate apparent immediate hazards to the subjects (need not seek prior IRB review and approval but must promptly notify the IRB of such changes). What this policy does not delineate are the procedures to be followed when an investigator implements a change to research – either intentionally or otherwise – without prior IRB review and approval and the change was not necessary to eliminate apparent immediate hazards to the subjects, e.g., protocol deviations. Given our prior determinations regarding (i) investigators initiating protocol changes without IRB review and approval (see June 9, 2009 letter; item (A)(2)); and (ii) failure of investigators to report unanticipated problems involving risks to subjects or others – unanticipated problems resulting from repeat protocol deviations (see June 9, 2009 letter; item (B)(2)) - we recommend that this policy, or Carle Foundation Policy 801, address what actions, if any, an investigator would be required to take once an investigator is made aware that such protocol deviations occurred, e.g., as a result of complaints, research team record reviews, internal or external audits, monitoring visit reports, or FDA 483 forms.

- (3) Carle Foundation Policy 403. According to this policy, all continuing review progress reports are to include specific information. We note, however, that this policy fails to list - as information that is required to be collected at continuing review - “any protocol violations that do not meet the prompt reporting requirements” We recommend that Carle Foundation Policy 801 state that such incidents be reported to the IRB at continuing review. We recommend that you correct this discrepancy.
- (4) Carle Foundation Policy 406. As currently written, this policy is limited to communicating IRB actions/decisions to the principal investigator. Please note that HHS regulations at 45 CFR 46.109(d) provide that an IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. As a result, we recommend that you expand this policy to include communicating such IRB actions/decisions to the institution in addition to the investigator.
- (5) Carle Foundation Policy 801. Many of the above-referenced comments relating to Carle Foundation Policy 403 pertain to this policy as well. We suggest revising the definitions of “minor protocol violations” and “protocol violations”. As currently written, it is not clear whether all protocol deviations not meeting the definition of “minor protocol violations” are considered “protocol violations.” Moreover, as currently written it is not clear whether the phrase “any departure from the protocol (violation or deviation) that causes harm to subjects or others, places them at increased risk of harm, impacts the scientific integrity, and/or has the potential to recur or represent possible serious or continuing noncompliance with the applicable federal regulations, guidance or IRB policies” constitutes a “minor protocol violation” or a “protocol violation.” Lastly, as currently written it is not clear when “minor protocol violations” and “protocol violations” are reportable to the IRB. We recommend that you revise this policy accordingly.

We determine that all of the corrective actions that have been identified and implemented by Carle Foundation adequately address the multiple determinations that we have made throughout this investigation. As a result, we are closing our investigation with your institution. Please notify us if you identify new information which might alter this determination.

We appreciate your institution’s continued commitment to the protection of human research subjects.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

March 15, 2011

cc:

Dr. James C. Leonard, Chief Executive Officer, Carle Foundation

Dr. Kendrith M. Rowland, Jr., Program Director, Carle Clinic Cancer Center

Dr. John R. Zech, Prior IRB Chairperson, Carle Foundation

Dr. N. Nadeem Ahmed, Current IRB Chairperson, Carle Foundation

Dr. Margaret A. Hamburg, Commissioner, Food and Drug Administration (FDA)

Dr. Joanne Less, FDA

Dr. Sherry Mills, NIH

Mr. Joseph Ellis, NIH

Dr. Harold Varmus, Director, NIH, NCI

Dr. Lori Minasian, NCI

Dr. Stephen Rosenfeld, Western Institutional Review Board