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June 9, 2009

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Carle Clinic Association
602 West University Avenue
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James C. Leonard, M.D.
Chief Executive Officer
Carle Foundation Hospital
611 West Park Street
Urbana, IL 61801

RE: Human Research Protections Under Federalwide Assurances FWA-5173 and 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 E5202

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 Mr. Bukosky and Dr. Leonard:

Thank you for your January 30, 2009 and February 18, 2009 reports in response to our January 6, 2009 and January 22, 2009 requests that the Carle Foundation Hospital (Carle Foundation) and the Carle Clinic Association (Carle Clinic) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). In addition, thank you for your March 13, 2009 excel spreadsheet in response to our February 18, 2009 email request that the Carle Foundation

institutional review board (IRB) (hereinafter referred to as the Carle IRB) provide us with a list of all currently active HHS-supported protocols approved by the Carle IRB. Lastly, we thank you for your March 6, 2009, March 19, 2009, May 5, 2009 and May 28, 2009 excel spreadsheets and March 9, 2009 and May 15, 2009 reports regarding studies for which IRB approval had lapsed.

We note that the Carle Foundation and the Carle Clinic decided to submit combined reports containing responses from both institutions. As a result, we have issued one determination letter to both institutions. We recognize that the Carle Foundation and Carle Clinic are two separate legal entities with two separate Federalwide Assurances (FWAs). We also recognize that the Carle Clinic designated the Carle IRB as an IRB authorized to review research covered by the Carle Clinic FWA in accordance with HHS regulations at 45 CFR 46.103(b).

[Redacted]

Based on the information submitted, we make the following determinations:

A. Determinations Regarding the Above-Referenced Research:

- (1) A complainant alleged, and we determine, that the Carle Foundation and the Carle Clinic collectively failed to prepare and maintain adequate documentation of IRB activities for the above-referenced research, in contravention of HHS regulations at 45 CFR 46.115(a) and 46.115(b).

HHS regulations at 45 CFR 46.115(a)(1) require that an institution, or when appropriate an IRB, shall prepare and maintain, among other things, copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators and reports of injuries to subjects. The regulatory provision at 45 CFR 46.115(b) requires that the records noted above shall be retained for at least 3 years after completion of the research and that all records must be accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner.

Our determination is based on the Carle Foundation/Carle Clinic response to this allegation. See January 30, 2009 report response to item (4). We note that the Carle

Foundation acknowledged that neither the Carle Foundation nor the Carle Clinic could locate/provide one or more of the following documents: IRB approved protocols, IRB meeting minutes, sample informed consent forms, continuing reviews/progress reports and/or protocol modifications for some of the above-referenced studies.

See additional questions and concerns (Sections E; F2, G and I) relating to adequate documentation of IRB activities for the above-referenced research.

Corrective Action: In order to address this noncompliance, the Carle Foundation has: (i) as of mid-2008, discontinued the practice of allowing the Carle Clinic to maintain copies of documents submitted to the Carle IRB relating to Carle Clinic Cancer studies and only making such documents available to the IRB/IRB staff as needed; (ii) required that all protocols and consent forms presented to the Carle IRB be retained in the Carle IRB files along with other Federally mandated information; (iii) developed a plan for the transfer of documents to the Carle IRB for all other Carle Clinic studies; and (iv) required more detailed minutes for IRB meetings. We note that the Carle Clinic deferred to the Carle Foundation's response to this allegation.

Required Action:

- (a) Please provide us with a corrective action that will ensure that the Carle IRB (as the reviewing IRB) and/or Carle Clinic retains Carle IRB records relating to Carle Clinic research for at least 3 years after completion of the research at the Carle Clinic as required by HHS regulations at 45 CFR 46.115(b).
 - (b) Please provide us with a final report once all IRB records are transferred to and maintained by the Carle IRB in accordance with the Carle Foundation's proposed corrective action.
- (2) A complainant alleged that an investigator initiated protocol changes without IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). 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. We determine that an investigator initiated certain protocol changes without IRB approval in circumstances where the changes were not necessary to eliminate apparent immediate hazards to the subjects. This determination is based on the fact that we found no documentation that the Carle IRB reviewed and approved the protocol changes noted in the October 24, 2008 North Central Cancer Treatment Group (NCCTG) Audit Report prior to the investigator initiating such changes.

Required Action: Please provide our office with a corrective action plan ensuring that Carle Clinic investigators will obtain IRB review and approval of 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. We note that the Carle Foundation and Carle Clinic

responses to OHRP did not address IRB review and approval of proposed changes in a research activity; instead, the responses focused on the reporting of protocol violations once they have occurred, the NCCTG Audit Report and corrective action plan.

- (3) A complainant alleged that Carle IRB members with conflicting interests participated in IRB review of research, in contravention of HHS regulations at 45 CFR 46.107(e). In specific, the complainant alleged that Carle Clinic doctors who are members of the Carle IRB are informed that their performance reviews and raises will take into account how easy (or hard) it is to obtain IRB approval of Community Clinical Oncology Program studies.

We reviewed the collective Carle Foundation and Carle Clinic response to this allegation, including affidavits from various Carle IRB members contesting this allegation. Based on this information, we determine that this allegation of noncompliance is unproven.

- (4) A complainant alleged that the informed consent of subjects enrolled in protocol ECOG E5202 was not obtained for collection of tissue specimens, and the Carle IRB did not waive consent for this research activity as required by HHS regulations at 45 CFR 46.116.

We reviewed the collective Carle Foundation and Carle Clinic response to this allegation. According to Carle Clinic, during the course of its investigation into this matter it was discovered that an employee from an affiliate site failed to have a subject complete the tissue collection section of the ECOG E5202 informed consent document when the affiliate site employee initially obtained informed consent from a subject on June 25, 2007. Once discovered, the subject, who was still at the affiliate site when the discovery was made, completed the tissue collection section of the informed consent document. Based on this information, we determine that this allegation of noncompliance is unproven.

- (5) A complainant alleged that both institutions lacked written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of any unanticipated problems involving risks to subjects or others, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5). We reviewed the collective Carle Foundation and Carle Clinic response as well as the following supporting documentation: Carle Foundation SOP RI 801 - IRB-Required Investigator Actions (effective date 6/1/06); Carle Foundation SOP: CO 602 – IRB Communications with Other Entities; Carle Clinic Policy 1307 – Reporting Safety Issues to IRB, the Food and Drug Administration (FDA), Clinical Trial Sponsors and the Human Protections Administrator (effective 4/15/07) and Carle Clinic Policy 1308 – Reporting Incidents to the office for Human Research Protections by the Clinic Human Protections Administration (effective 4/10/06). Based on our review, we find that both institutions have appropriate written procedures regarding such reporting, and thus determine that this allegation of noncompliance is unproven.

B. Additional Determinations:

- (1) We determine that the Carle IRB did not conduct continuing review of research at least once per year as required by HHS regulations at 45 CFR 46.109(e) and that Carle Clinic investigators continued to conduct non-exempt human subjects research activities beyond the expiration date of IRB approval. This determination is based on various excel spreadsheets; a March 9, 2009 report, a March 20, 2009 email correspondence, and a May 15, 2009 report. We note that all of these documents were submitted to our office after we sent Carle Foundation a February 18, 2009 email requesting that the Carle IRB forward to us a list of all currently active HHS-supported protocols approved by the Carle IRB; the list was to include protocol title; principal investigator's name; date of initial IRB approval; type of IRB review (expedited or full board); dates of all subsequent IRB continuing reviews and the type of continuing review (expedited or full board).

We note the following from the March 9, 2009 letter: “While we understand that according to OHRP guidance there is no obligation to report studies for which IRB approval has lapsed due to failure to obtain timely continuing review, in light of the recent allegations made to OHRP, and in the spirit of full disclosure, we are voluntarily reporting this finding from our internal investigation.” Please note that the OHRP guidance document entitled “Guidance on Continuing Review” only addresses the issue of whether an expiration of IRB approval needs to be report to OHRP as a suspension of IRB approval; the guidance document does not discuss whether the reporting of such incidents is required under another reporting obligation. Please note that HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) requires that an institution promptly report to the IRB, appropriate institutional officials, the department or agency head and OHRP of, among other things, any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB.

Corrective Action: We acknowledge the following Carle Clinic corrective action plan noted in the March 9, 2009 report:

- (a) Transitioning IRB review of Carle Clinic studies to an independent IRB;
- (b) Carle Clinic’s use of an electronic protocol tracking system;
- (c) Dedicating a Carle Clinic secretary to IRB related issues;
- (d) Adoption of a “double check” system;
- (e) Change from 11 month to 10 month approval cycle;
- (f) Establishment of Carle Clinic policy and/or procedure development regarding closures, lapsed studies, continuing reviews and affiliates;
- (g) Training IRB secretaries and appropriate staff; and
- (h) Internal audit of continuing review process.

Required Action: Please provide us with a copy of the final policy/procedure regarding closures, lapsed studies, continuing reviews and affiliates mentioned in the March 9, 2009 report under Corrective Action Plan, item 6 and the final report noted in the March 20, 2009 email.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5) require that an institution have written IRB procedures that adequately describe certain delineated activities. We reviewed the Carle Clinic Policy 1307 – Reporting Safety Issues to IRB, FDA, Clinical Trial Sponsors and the Human Protections Administrator (effective 4/15/07) and the Carle Clinic Policy 1308 – Reporting Incidents to the office for Human Research Protections by the Clinic Human Protections Administration (effective 4/10/06), and we specifically note the following sections of those policies:

- (a) Carle Clinic Policy 1307 requires an investigator to
 - (i) Report to the Carle Clinic Human Protections Administrator (HPA) serious or continuing noncompliance with Federal regulations; complete a research incident report and submit such report within five working days of acquiring knowledge of noncompliance (See Policy Exhibit A);
 - (ii) Promptly report unanticipated problems involving risks to subjects or others to both the IRB and Clinic’s HPA (See Policy Exhibit A);
 - (iii) Promptly or as otherwise required by the IRB report protocol deviations to the IRB (See Policy Exhibit A).
- (b) Carle Clinic Policy 1308 states that the Clinic will comply with its FWA and 45 CFR 46.103(b)(5) by promptly reporting to OHRP, among other incidents, unanticipated problems involving risks to subjects or others and continuing noncompliance with Federal regulations or the requirements or determinations of the IRB. This policy defines continuing noncompliance to mean a situation in which there have been repeated instances of failure to follow Federal regulations and/or IRB policies and procedures.

We determine that the Carle Clinic did not comply with these procedures regarding the reportable events noted above at (A)(2) and (B)(1) of this letter. Moreover, we determine that this failure to follow such procedures resulted in the Carle Clinic’s failure to promptly report to OHRP unanticipated problems involving risks to subjects or others and serious or continuing noncompliance with HHS regulations at 45 CFR part 46, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). Of note, we are in receipt of documents indicating that, as early as November 2008, both the Carle IRB and individuals at the Carle Clinic were aware of:

- (a) Final NCCTG Audit Report results revealing unanticipated problems involving risks to subjects or others occurring in multiple studies, e.g., 12 major deficiencies associated with patient care issues; and
- (b) Continuing noncompliance, namely systemic problems involving lapses in continuing review of numerous Carle Clinic cancer studies.

Notwithstanding this knowledge, the Carle Clinic did not report the NCCTG Audit Report results regarding unanticipated problems to our office. Moreover, the Carle Clinic only reported the continuing noncompliance involving lapses in continuing review to our office after the Carle IRB received a February 18, 2009 email from us asking for a list of

all currently active HHS-supported protocols approved by the Carle IRB, including dates of initial IRB approval and dates of all subsequent IRB continuing reviews. As stated above, the Carle Clinic had knowledge of such continuing noncompliance since early November 2008.

Required Action: Please provide us with a corrective action that will ensure that the Carle Clinic will follow its written procedures for prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5).

- (3) HHS regulations at 45 CFR 46.103(b)(4) and (5) require that an institution have written IRB procedures that adequately describe certain delineated activities. HHS regulations at 45 CFR 46.108(a) require that each IRB shall follow written procedures in the same detail as described in HHS regulations at 45 CFR 46.103(b)(4) and to the extent required by HHS regulations at 45 CFR 46.103(b)(5). We have reviewed the Carle IRB written procedures (presented to us as having been implemented on December 20, 2006) and determine that although the Carle IRB had such written procedures, the Carle IRB did not follow those procedures for the following activities:
 - (a) Documentation Management. The practice of allowing Carle Clinic cancer investigators to maintain copies of documents submitted to the Carle IRB and only make such documents available to the IRB staff as needed contradicts procedure FO 305 – “Documentation and Document Management” (effective date: 6/1/06) - one of the procedures included in the document entitled “Policies for the Carle Institutional Review Board” (implemented at the Carle Foundation on December 20, 2006). In specific, we note that the “Documentation and Document Management Policy Statement” provides that “The IRB’s files must be maintained in a manner that contains a complete history of all IRB actions related to review and approval of a protocol, including continuing reviews, amendments and adverse event reports. We also note that the Scope Section of this procedure states that “The policies and procedures apply to all controlled documents used in the submission, initial review and continuing review of research under the jurisdiction of the IRB.”
 - (b) Continuing review. The subcommittee continuing review process, as explained during the January 23, 2009 Carle IRB meeting, conflicts with the following Carle IRB Policies/Procedures, which took effect on 12/20/06:
 - (i) SOP: FO 301 – “Research Submission Requirements,” which provides that 60 days prior to the IRB approval expiration date, investigators requesting renewal of an approved research project must submit a completed continuing review report and renewal request (Form RR 404-A). We note that this procedure applies to all research submitted to the IRB;

(ii) SOP: FO 303 – “IRB Meeting Administration” states as follows:

- The IRB may by majority action approve the implementation of a primary reviewer panel system for certain types of research. Such determination shall be recorded in the minutes as an official act of the IRB. The IRB shall advise the institutional official (IO) and obtain the concurrence of the IO.
- That each member of the IRB, whether or not a member of the primary reviewer panel, shall receive at least the informed consent and a summary of the protocol in sufficient detail to permit the IRB member to understand the basics of the proposed research, and to compare the research-specific provisions of the informed consent to the protocol. We note that this procedure applies to all research submitted to the IRB.

(iii) SOP: FO 304 – “Administration Review and Distribution of Materials” states that copies of application materials described in SOP FO 301 “Research Submission Requirements” will be distributed to all IRB members sufficiently in advance to allow reasonable time for review, and that each regular member of the IRB will receive a copy of the research documents. We note that this procedure applies to all research submitted to the IRB.

(iv) SOP: RR 404 – “Continuing Review – Criteria for Renewal” provides that in order to evaluate a study for renewal of approval, the following will be reviewed: the currently approved consent document; written notification from the investigator advising the IRB as to whether he/she believes new findings that may relate to the subject’s willingness to continue participation have developed, and whether any additional or revised information should be provided to subjects in an updated consent form; current approved protocol including any amendments to the protocol since initial review; a separate cover letter describing in detail each change and all appropriate documentation must accompany the continuing review application. This SOP continues that each IRB member shall receive a progress report prepared and submitted by the investigator. This progress report is to include, among other information, unanticipated problems involving risks to subjects or others; withdrawal of subjects since last review; complaints about the study since last review; a summary of recent literature relevant to the research; and an updated assessment of the risk to benefit ratio which takes into account the above factors.

Required Action: Please provide us with a corrective action that will ensure that the Carle Foundation will abide by its written IRB procedures as required by HHS regulations at 45 CFR 46.103(b)(4) and (5) and 46.108(a). In addition, we note that Carle IRB SOP: “FO 303 – IRB Meeting Administration,” provides that the IRB may approve the implementation of a primary reviewer panel system for certain types of research. The procedure states that such a determination shall be recorded in the minutes as an official act of the IRB, and that the IRB shall advise the IO and obtain the concurrence of the IO. Please provide us with the documentation referenced in this IRB procedure.

C. Questions and Concerns Regarding the Above-Referenced Studies:

(1) [Redacted]

(2) [Redacted]

[Redacted]

- (ii) Addendum 5 was reviewed and approved by the Carle IRB on that same date, January 16, 2008;
- (iii) Addendum 5 was approved at the January 16, 2008 IRB meeting which was called to order at 7:40 a.m.;

(3) [Redacted]

[Redacted]

(4) [Redacted]

[Redacted]

(5) [Redacted]

[Redacted]

D. Questions and Concerns Regarding ECOG E5202 (Carle IRB Number 08-42)

[Redacted]

E. Questions and Concerns Regarding RTOG 0522 (Carle IRB Number 08-57)

[Redacted]

F. Questions and Concerns Regarding NSAPB B-36 (Carle IRB 08-18)

[Redacted]

[Redacted]

(2) [Redacted]

[Redacted]

G. Questions and Concerns Regarding CTSA CALGB 40101 (Carle IRB 08-06)

[Redacted]

H. Questions and Concerns Regarding CTSU SWOG S0221 (Carle IRB 08-10)

[Redacted]

[Redacted]

I. Questions and Concerns Regarding NCCTG N01C5 (Carle IRB 08-267)

[Redacted]

J. Questions and Concerns Regarding NCCTG N0489 (Carle IRB 08-277)

[Redacted]

[Redacted]

(2) [Redacted]

K. Questions and Concerns Regarding NCCTG R0525 (Carle IRB 08-64)

[Redacted]

[Redacted]

[Redacted]

L. Questions and Concerns Regarding NCCTG N0338 (Carle IRB 08-376)

[Redacted]

M. Questions and Concerns Regarding Carle Foundation's System for Protecting Human Subjects

[Redacted]

[Redacted]

(2) [Redacted]

(3) [Redacted]

N. Recommendations:

- (1) Although this is not required by 45 CFR part 46, we recommend that the Carle IRB consider implementing a policy that bans Cancer Clinic staff from attending IRB meetings during the IRB deliberative process. It has come to our attention that IRB members have asked that such staff leave the IRB meeting room at the time of deliberation so that the IRB members can deliberate confidentially. Notwithstanding this request, Cancer Clinic staff have remained in the IRB meeting room.
- (2) We recommend that the Carle Clinic revise the definition of “unanticipated problems involving risks to subjects or others” in Policy 1308. The current policy inappropriately defines “unanticipated problems involving risks to subjects or others to mean those events, situations or outcomes not identified in the IRB application and informed consent document that cause harm (emphasis in original) to physical, psychological or financial well being ...” The HHS regulations for the protection of human subjects at 45 CFR 46.103(b)(5) require the reporting of unanticipated problems involving risks to subjects or others regardless of whether the risks result in actual harm; the concept of “harm” is not part of the regulatory term. We also note that the understanding of the Carle IRB regarding the term “unanticipated problems involving risks to subjects or others” may be misplaced. This observation is based on the repeated statements by the IRB as to whether subjects experienced harm as a result of various noted protocol deviations. See February 13, 2009 IRB meeting minutes. We wish to clarify that whether or not the subjects experience harm as the result of a protocol deviation is not relevant to the question of whether that protocol deviation represents an unanticipated problem involving risks to subjects or others. For further guidance, please refer to our *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, available at <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>
- (3) We recommend that the Carle Clinic name a new Human Protections Administrator (HPA), or designate a secondary HPA when an investigator may also be the HPA. We note that currently the Carle Clinic HPA is also the principal investigator in all of the above-referenced studies; we believe that this dual appointment may present a potential conflict of interest when the HPA is responsible for reporting noncompliance that may involve his/her own studies
- (4) HHS regulations at 45 CFR 46.103(b) require, in part, that a Federalwide Assurance shall include designation of one or more IRBs established in accordance with the requirements of the regulations, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties. We note that three of the

major deficiencies relating to protocol deviations and regulatory noncompliance that were noted in the final NCCTG Audit Report occurred at non-Carle Foundation sites, i.e., Rush Copley, Joliet, and Michiana: one of which has a deactivated FWA as of 9/2/08. We also note the following discussion from the minutes of a February 18, 2009 Carle IRB meeting in reference to IRB 08-64, a study involving oversight of research being conducted at a non-Carle Foundation site:

- (a) The IRB asked for specific information about the identity of researchers at the affiliate site and an assurance that there is a medical doctor overseeing the consent process at that site;
- (b) The IRB asked whether regular visits to affiliate sites are made by the Carle Clinic Cancer Center principal investigator and whether a contract research associated (CRA) does oversight at those sites; and
- (c) The IRB agreed that an oversight plan for affiliate sites, with site-specific plans for human subject protections, a list of researchers, and documentation of researcher training should be provided by the principal investigator by June 2009.

In light of this information, we recommend that the Carle IRB: (i) develop an IRB plan for approving research being conducted at non-Carle Foundation sites and monitoring of such research once approval has been granted (e.g., procedures used for ensuring that non-Carle Foundation site employees are qualified to conduct research, sites have the infrastructure/resources needed to conduct the research, etc); (ii) revisit its IRB authorization agreements between the IRB and the institutions that designate the Carle IRB to be the IRB of record; and (iii) revise such IRB authorization agreements in light of the new approval/oversight plan.

Please provide us with responses to the above determinations and questions and concerns by July 7, 2009. Please note that it is our understanding that this research was funded in part by a cooperative agreement with the National Institutes of Health (NIH). NIH may have additional requirements for funding based upon the timely and appropriate response to our determinations.

If you identify any noncompliance during your review of the above determinations and questions and concerns, please describe any corrective actions that have been and will be taken to address the noncompliance.

Please don't hesitate to contact me if you have any questions or need assistance in developing any corrective action plan.

Sincerely,

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

cc :

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

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

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

Ms. Barbara Zachow, Research Office Supervisor, 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. John E. Niederhuber, Director, NIH, National Cancer Institute (NCI)

Dr. Lori Minasian, NCI

Ms. Joan Mauer, NCI

Dr. Angela Bowen, Western Institutional Review Board