



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-8120
FAX: 240-453-6909
E-mail: Lisa.Rooney@hhs.gov

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Bruce Wellman, M.D.
Chief Executive Officer
Carle Clinic Association
602 West University Avenue
Urbana, IL 61801

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 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 Drs. Wellman and Leonard:

As you know, earlier this year the Office for Human Research Protections (OHRP) initiated a compliance oversight evaluation of the Carle Foundation Hospital (Carle Foundation) and Carle Clinic Association (Carle Clinic) concerning the above-referenced research. We thank you for the July 7, 2009 Carle Foundation report and the July 13, 2009 Carle Clinic report in response to our June 9, 2009 letter, which included determinations, questions, and concerns that were based

on written information that was submitted to our office. Moreover, as you are aware, our office subsequently conducted an on-site evaluation of the Carle Foundation and the Carle Clinic human subject protection programs on July 28-30, 2009. The evaluation, conducted by five OHRP staff with the assistance of three consultants and two National Cancer Institute (NCI) staff members, included meetings with the Carle Foundation FWA Signatory Official, the current and prior Carle Clinic FWA Signatory Officials, the Carle Foundation Institutional Review Board (Carle IRB) chairpersons and members, research staff members, and investigators who are or were supported by the Department of Health and Human Services (HHS). The on-site evaluation involved review of IRB files for 43 protocols and IRB meetings minutes from 2004 – 2009.

In the course of the OHRP on-site evaluation, the IRB members, IRB staff, and investigators displayed an enthusiastic and sincere concern for the protection of human subjects.

Based on the information contained in your July 7, 2009 and July 13, 2009 reports, interviews conducted during the on-site evaluation, and information reviewed during the on-site evaluation, we make the following determinations:

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

- (1) In our June 9, 2009 letter, we determined 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). As a result of this determination, we asked the Carle IRB and/or Carle Clinic to provide us with a corrective action plan that will ensure that the Carle IRB and/or Carle Clinic retains IRB records relating to Carle Clinic research for at least 3 years after completion of the research at the Carle Clinic.

Carle Foundation Corrective Action: We acknowledge that the Carle Foundation has taken or will take the following actions in order to ensure that the Carle IRB retains complete research records:

- (a) Revised its IRB procedure entitled “Documentation and Document Management” (IRB 303) in order to specify the types of documents that must be maintained by the Carle IRB for at least three years after completion of research.
- (b) Is compiling complete study histories for all research that underwent Carle IRB review. We understand that as of July 7, 2009, the Carle Foundation:
 - Received study histories for 34 of 35 open Carle Clinic studies;
 - Requested study histories for 156 closed Carle Clinic studies (histories to be submitted to the Carle IRB electronic system by August 21, 2009); and
 - Will request study histories for all Carle Clinic studies that have been closed for more than a year and are located in paper format only.

- (c) Retained an external auditor to review Carle IRB files and initiated plans to hire an internal auditor who will be responsible for, among other things, monitoring IRB records to verify compliance with IRB policies and applicable Federal requirements.
- (d) Will continue to train Carle IRB staff on maintenance of IRB records in accordance with Federal regulations and Carle IRB procedure IRB 303.

Carle Foundation Required Action: Please provide us with a final report describing the study histories for the 156 closed Carle Clinic studies, which histories were to be submitted to the Carle IRB electronic system by August 21, 2009, and the study histories for all Carle Clinic studies that have been closed for more than one year once these study histories have been received by the Carle IRB.

Carle Foundation Recommended Action: We recommend that the Carle Foundation revise its IRB policy entitled “Documentation and Document Management” to specify the retention requirements for records relating to research which is never conducted, e.g., either never approved, or approved but no subjects were ever enrolled. Please note that HHS regulations at 45 CFR 46.115(b) state that the records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of research. For example, Carle Foundation may want to consider revising its policy to state that records relating to research which is never conducted shall be retained for at least 3 years from the last IRB correspondence or action relating to such research.

Carle Clinic Corrective Action: We understand that the Carle Clinic is in the process of providing the Carle Foundation IRB with complete study histories for the following Carle Clinic studies that had been reviewed/approved by the Carle IRB: (a) all currently active/open studies; and (b) all studies that have been closed within the last three years. We acknowledge that the Carle Clinic has established a policy requiring that the Carle Clinic maintain records pertaining to Carle Clinic studies in accordance with 45 CFR 46.115. Lastly, we note that the Carle Clinic is currently drafting one or more IRB Authorization Agreements which, among other things, will outline which entity, i.e., the institution or IRB, will be responsible for the maintenance of IRB records.

Carle Clinic Required Action: Please provide us with copies of any IRB Authorization Agreements that are ultimately executed by the Carle Clinic.

- (2) In our June 9, 2009 letter we determined that an investigator initiated protocol changes without IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii), which 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. As a result of this determination, we requested that both Carle Foundation and Carle Clinic provide us 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.

Carle Foundation Corrective Action: We acknowledge that the Carle Foundation has taken or will take the following actions in order to address the above determination:

- (a) Revised the Carle IRB template continuing review approval letter to highlight the fact that investigators are required to obtain prospective IRB approval of certain changes to research.
- (b) Revised the Carle IRB policy entitled “Ongoing Oversight” (IRB 403) to be in compliance with HHS regulations at 45 CFR 46.103(b)(4)(iii).
- (c) Will develop on-line training (to be available in September 2009) to ensure that all investigators and research staff are familiar with the IRB policy and procedures regarding this issue.
- (d) Will require investigators to provide an assurance, when submitting an initial or continuing review application, that they are familiar with all current Carle IRB policies.
- (e) Retained an external auditor to review IRB and investigator files and initiated plans to hire an internal auditor who will be responsible for, among other things, monitoring IRB records to verify that investigators do not implement protocol changes without IRB approval.
- (f) Revised the Carle IRB Application for Review of Research to include an assurance by the investigator that s/he will permit the Carle IRB to audit the investigator’s research project and notice that refusal to permit audits by the Carle IRB will result in suspension and possible termination of the IRB’s approval of the research.
- (g) Will forward a statement from the Carle Foundation FWA Signatory Official regarding the importance of compliance with the IRB’s policies regarding human subjects protection and the actions that may be taken to enforce compliance with the policies to the Carle IRB research community.

Carle Foundation Required Action: We note that Attachment A of your July 7, 2009 report only includes the Carle IRB template for continuing review and approval. Please ensure that the Carle Foundation also revises the Carle IRB template for initial review and approval to inform investigators at the time of initial approval that they are required to obtain prospective IRB approval of all changes to a research protocol, except when necessary to eliminate apparent immediate hazards to the subjects.

Carle Clinic Corrective Action: We note that the Carle Clinic has provided our office with a copy of Carle Clinic Policy 5308 entitled “Reporting Safety Issues to IRB, FDA, Clinical Trial[s] Sponsors & the Human Protections Administrator” as the current policy addressing the requirement that investigators 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 this policy does not explain what steps the investigator must take when s/he prospectively anticipates making a change to an IRB-approved protocol. Instead, the current policy only appears to provide guidance to investigators when an investigator realizes that s/he has inadvertently amended a protocol. Of note, the policy provides the following in reference to protocol deviations (any exceptions from the design or procedures)/protocol amendments: investigator must promptly report such deviations/amendments to the IRB (or as otherwise required by the IRB).

Carle Clinic Required Action: Please revise the above-referenced policy, or draft a new policy, to address those instances where an investigator prospectively anticipates making a change to an IRB-approved protocol. In addition, provide us 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.

- (3) In our June 9, 2009 letter we determined 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. As a result of this determination, we asked the Carle IRB and Carle Clinic to provide us with a copy of the final policy/procedure regarding closures, lapsed studies, continuing reviews and affiliates mentioned in the Carle Clinic March 9, 2009 report under Corrective Action Plan, item 6 and the final report noted in the Carle Foundation March 20, 2009 email.

Carle Foundation Corrective Action: We recognize that the Carle Foundation has taken or will take the following actions in order to ensure that the Carle IRB conducts continuing review of research at least once per year as required by HHS regulations at 45 CFR 46.109(e) and that investigators do not conduct non-exempt human subjects research activities beyond the expiration date of IRB approval:

- (a) Implemented an electronic IRB system which automatically notifies investigators when a study must be submitted for continuing review and when IRB approval of a study has expired.
- (b) Drafted a policy entitled “Project Closure or Transfer” (IRB 405) which explains that upon expiration of approval a study is considered closed and must be resubmitted as a new study if the investigator wishes to continue the study.
- (c) Revised the Carle IRB policy entitled “Continuing Review” (IRB 404) to clarify that once approval of a study has lapsed, investigators must stop all research activities involving human subjects, except where the investigator determines that it is in the best interests of enrolled subject to continue participation.

- (d) Will utilize the services of the external auditor to identify any incidents where investigators continue to conduct non-exempt human subjects research activities after expiration of IRB approval so that action by the IRB may be taken.
- (e) Provided a final report of the current status of the 127 lapsed studies noted in the March 20, 2009 email.

Carle Foundation Required Action: Please provide our office with the status of all of the studies noted in Attachment D of the Carle Foundation July 7, 2009 response that are **not** noted as having been closed by the Carle IRB or closed with the Carle IRB. For example, please provide us with the status of NCCTG N0032. According to Attachment D, this study lapsed on June 18, 2009, and 15 non-exempt human subjects research activities occurred after this lapse in IRB approval. We note further that on June 25, 2009, the IRB requested further information from the investigator regarding this study and its lapse in IRB approval. It is not clear from the information contained in Attachment D whether this study was ultimately closed by the Carle IRB, closed with the Carle IRB, re-approved by the Carle IRB, or transferred to the external IRB for review and approval.

Carle Clinic Corrective Action: We acknowledge receipt of the above-referenced Carle Clinic policies/procedures. We recognize that the Carle Clinic will take the following actions in order to ensure that the Carle Clinic investigators do not conduct non-exempt human subjects research activities beyond the expiration date of IRB approval as required by HHS regulations at 45 CFR 46.109(e):

- (a) Transition all federally-funded Carle Clinic studies to an independent IRB;
- (b) Implement an electronic protocol tracking system;
- (c) Dedicate a Carle Clinic secretary to IRB related issues;
- (d) Adopt a “double check” system;
- (e) Implement a 60-day reminder notice to identify which studies are subject to continuing review within the next 60 days;
- (f) Train IRB secretaries and appropriate staff on the policies/procedures of the independent IRB, the Carle Clinic electronic system; and
- (g) Conduct internal audits of the continuing review process.

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

- (4) In our June 9, 2009 letter we determined that the Carle Clinic did not comply with Carle Clinic Policy 1307 and Carle Clinic Policy 1308 regarding the reporting of unanticipated problems involving risks to subject or others and continuing noncompliance with the regulations. Moreover, we determined 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).

Carle Clinic Corrective Action: We acknowledge that the Carle Clinic is embarking on an effort to retrain all of its investigators, relevant staff, and its Signatory Official on Carle Clinic human subject protections policies/procedures, the policies and procedures of the external IRB(s) designated under the Carle Clinic FWA, as well as HHS regulations governing the protection of human subjects. In addition, we note that the Carle Clinic is establishing an annual research audit program which will include, among other things, the identification of serious and/or continuing noncompliance with HHS regulations at 45 CFR part 46 or the requirements or determinations of the IRB.

Carle Clinic Required Action: Please provide our office with documentation of all training that was completed by the anticipated August 31, 2009 completion date as well as a final outline/description of the Carle Clinic Research Audit Program.

- (5) In our June 9, 2009 letter we determined that the Carle IRB did not follow certain 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), in violation of HHS regulations at 45 CFR 46.108(a). As a result of this determination, we asked the Carle Foundation to provide us with a corrective action plan 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 asked the Carle Foundation to provide us with documentation referenced in Carle IRB SOP: “FO 303 – IRB Meeting Administration,” regarding the implementation of a primary reviewer panel system for certain types of research.

Carle Foundation Corrective Action: We recognize that the Carle Foundation has taken or will take the following actions to ensure that the Carle IRB follow its 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):

- (a) Revised the Carle IRB policy entitled “IRB Meeting Administration” (IRB 302) to clarify the processes for appointment of primary reviewers and responsibilities of such reviewers as well as all other IRB members;
- (b) Educated its IRB members on current IRB policies, regulations and guidance documents and provided these members with a binder containing all such policies/regulations and guidance documents;
- (c) Conduct periodic audits of the IRB processes to determine whether the Carle IRB is adhering to its written procedures; audits results will be communicated to Human Subjects Protection (HSP) Program Director, IRB Chairperson, and Carle Foundation’s FWA Signatory Official and Compliance Officer
- (d) Continue to encourage continuing education for HSP staff and IRB chairpersons.

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

Carle Clinic Corrective Action: We appreciate the steps that the Carle Clinic has taken to ensure that Carle Clinic investigators and staff are knowledgeable about both Carle Clinic IRB policies/procedures as well as the policies/procedures of other IRB(s) designated on the Carle Clinic FWA. Please note, however, that this particular determination was directed to the Carle Foundation; thus the Carle Clinic did not have to respond to this determination

B. Additional Determinations Regarding the Above-Referenced Research:

In addition to the determinations noted above, we make the following determinations regarding the above-referenced research:

- (1) We determine that the Carle IRB, when reviewing the above-referenced protocol applications, lacked sufficient information to make some of the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, when reviewing certain protocols, the IRB reviewed insufficient information regarding the informed consent process, including subject recruitment and enrollment procedures, and the provisions to protect the privacy of subjects and maintain the confidentiality of data at the Carle Clinic site. This determination is based on the fact that the IRB records for all of the above-referenced protocols were silent as to the informed consent process and the provisions to protect the privacy of subjects and maintain the confidentiality of data at the Carle Clinic site, i.e., such issues are not addressed in the IRB submission forms, protocols, or informed consent documents.

Carle Foundation Corrective Action: We acknowledge that the Carle Foundation has taken or is taking the following corrective actions to ensure that the Carle IRB only approves research after the IRB has obtained sufficient information to make all determinations required for approval of research under HHS regulations at 45 CFR 46.111:

- (a) Revised the Carle IRB Application for Review of Research (in use since January 2009) to specifically require investigators to
 - (i) Provide information regarding when, where, how and by whom consent (including parental permission/assent) will be obtained; how subjects will be given sufficient opportunity to consider whether to consent; and what steps will be taken to minimize the possibility of coercion or undue influence; and
 - (ii) Explain what precautions will be taken to protect the privacy of subjects and the confidentiality of identifiable information; how and where data will be kept, and if and when it will be destroyed and how study personnel will be trained regarding the handling of confidential information.

- (b) Implemented an IRB reviewer checklist for use by IRB members in their review of research protocols; the checklist includes, among other considerations, references to the informed consent process, recruitment of subjects, and maintenance of the privacy of study subjects and the confidentiality of study data;
- (c) Revised the Carle IRB policy entitled IRB Meeting Administration (IRB 302) to specify that meeting minutes should include references to determinations, review of the measures described in the protocol to protect privacy of subjects and confidentiality of data, and the informed consent approval/waiver process;
- (d) The HSP staff will begin implementing a function available through the electronic IRB system that permits staff to develop and use a template for IRB minutes; the template will include prompts relating to topics that must be discussed for each study reviewed; and
- (e) Initiated plans to hire an internal auditor who will be responsible for monitoring IRB records and IRB meeting minutes to confirm that the IRB received all required documents and that IRB minutes reflect the information required by the regulations.

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

Carle Clinic Response: We acknowledge that the Carle Clinic did not provide a response to this concern given that the concern involved information regarding the Carle IRB deliberative process to which the Carle Clinic was not privy. Notwithstanding this concern, we note that the Carle Clinic has transferred all of its HHS-funded research to an external IRB and as of July 9, 2009, a vast majority of Carle Clinic's HHS-funded research, i.e., 212 of 225 studies, had been re-reviewed and approved by the external IRB.

- (2) In our June 9, 2009 letter we raised a concern regarding whether Carle Clinic investigators initiated research without IRB approval, in contravention of HHS regulations at 45 CFR 46.109(a); in specific, that investigators recruited subjects into specific protocols before IRB review and approval of those protocols occurred.

We acknowledge that the Carle Clinic has interviewed numerous individuals regarding this concern and has been unable to identify any instances when Carle Clinic investigators recruited subjects prior to IRB approval. Given the above explanation, we determine that this allegation of noncompliance is unproven.

C. Additional Determinations Regarding the Carle Foundation and Carle Clinic Human Subjects Protection Programs:

In addition to the determinations noted above, we make the following determinations regarding your institutions' human subjects protection programs:

- (1) A complainant alleged that both the current Carle Foundation Signatory Official and the prior Carle Clinic Signatory official failed to fulfill their obligations under the HHS regulations at 45 CFR 46.103(c) and the terms of the institutions' FWA. In specific, a complainant alleged that the HSP Program Director (September 2008) and the Vice President for Research (November 2008) of the Carle Foundation were fired after each of these individuals made attempts to bring the research at your respective institutions into compliance with HHS regulations at 45 CFR part 46.

We have received documentation indicating that as early as November 2008 both of you, as FWA Signatory Officials, were aware of the following:

- (a) A memorandum dated November 18, 2008 regarding a July 29-30, 2008 North Central Cancer Treatment Group (NCCTG) Audit Report, a scheduled internal IRB audit on the files that were the subject of the NCCTG Audit Report to be conducted on November 20, 2008, and the firing of the Carle Foundation Hospital Vice President for Research – the person requesting that such an audit occur - the day after the November 18, 2008 letter was forwarded to the Carle Foundation FWA Signatory Official for review;
- (b) The fact that the scheduled November 20, 2008 internal IRB audit was never completed on the NCCTG audited files as indicated in the above-referenced November 18, 2008 letter, although the NCCTG Audit Report revealed major deficiencies involving enrolled subjects;
- (c) The failure of the Carle IRB to review and take action on the NCCTG Audit Report findings, which revealed unanticipated problems involving risks to subjects and others, until after both of your institutions received an inquiry letter from our office inquiring about such audit findings;
- (d) The failure to report to our office the NCCTG Audit Report findings revealing unanticipated problems involving risks to subjects and others and continuing noncompliance regarding failure to obtain continuing review;
- (e) Problems between the Carle IRB and a Carle Clinic Cancer Center investigator without providing the Carle IRB with support to address the problems;
- (f) A lack of adequate IRB policies and procedures;
- (g) The need for additional IRB staff – of note “The staff (IRB) seems very stressed and overworked and admitted that they can’t keep up.” See November 13, 2008 email from Carle Clinic Chief Operating Officer to the Carle Foundation Vice President for Research and carbon copying, among others, the Carle Foundation Signatory Official.

In addition, we note that, during our July site visit, in an interview with you and the prior Carle Clinic Signatory Official, it was stated to the site visit team that, prior to November 2008, neither Signatory Official was aware of the regulatory responsibilities of a Signatory Official.

HHS regulations at 45 CFR 46.103(c) require that an institution’s assurance of compliance with the regulations for the protection of human subjects shall be executed by

an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the regulations. Given the above, we determine that the current Carle Foundation Signatory Official and prior Carle Clinic Signatory Official failed to fulfill the obligations imposed by the HHS regulations for the protection of human subjects and the institutions' FWAs as required by HHS regulations 45 CFR 46.103(c).

Carle Clinic Corrective Action: We acknowledge the following from the Carle Foundation response:

- (a) Before we opened our case with the Carle Foundation and Carle Clinic, we note that the Carle Foundation Signatory Official allowed the HSP Director and Vice President (VP) for Research to implement certain operational and procedural changes improving Carle Foundation's human subjects protections program and the timely exchange of information between Carle Foundation and Carle Clinic;
- (b) While the Carle Foundation Signatory Official was aware of the NCCTG audit results in November 2008, he determined that prior to an internal audit of the protocols identified in the NCCTG audit, it would be beneficial to meet with Carle Clinic executives to discuss the issues raised in the NCCTG audit report. We note that there were multiple meetings between research officials and staff at both institutions, but that the meetings focused on how to facilitate the IRB review process rather than addressing the NCCTG audit results;
- (c) On December 12, 2008, the Carle Foundation Signatory Official met with the Interim Director of HSP to talk about Carle Foundation IRB compliance issues and directed her to develop a detailed proposal for improving IRB compliance. We note that this meeting resulted in a December 30, 2008 letter outlining proposed solutions to the identified IRB compliance issues. We note further that this proposed plan was subsequently submitted to the Carle Foundation's Board of Directors on January 9, 2009 and that most of the proposed measures were implemented shortly thereafter; and:
- (d) On April 30, 2009, the Carle Foundation Signatory Official underwent training that addressed Signatory Official obligations.
- (e) During an interview conducted during our July site visit, the Carle Foundation Signatory Official recognized a lack of understanding of his regulatory responsibilities, and stated to the site visit team that the Carle Foundation Signatory Official now fully understood the role of the Signatory Official and was committed to fulfilling that role.

Carle Foundation Required Action: Given the concerns relating to the behavior of the current Signatory Official, we are requiring that the Carle Foundation provide quarterly reports to our office regarding implementation of the corrective actions identified in this letter. In particular, please provide us with updates regarding the Carle Foundation Auditing Program, i.e., the program that will monitor IRB processes as well as IRB and investigator files. In specific, please ensure that this update includes: (1) the number of

files reviewed; (2) findings; and (3) any proposed corrective actions. Moreover, given the possible impending merger between Carle Clinic and Carle Foundation, we are requiring that the Carle Foundation provide quarterly reports to our office regarding the merged organizations' future plans for the protection of human subjects. Please forward the quarterly reports to Lisa Rooney (see letterhead address) until further notice. Please submit the first quarterly report to our office on December 15, 2009. This report should cover all quarterly report related activities that have occurred between September 1, 2009 and November 30, 2009.

Carle Clinic Corrective Action: We acknowledge the Carle Clinic response to this allegation. In particular, we acknowledge that the Carle Clinic has named a new Signatory Official on its FWA and that this new Signatory Official has taken numerous training programs specific to human subject protections and Signatory Official responsibilities. It is our understanding that the new Signatory Official will require all research audit findings to be reported to him and the new Human Protections Administrator so that these individuals can monitor the reporting of such research audit findings to the designated IRB and OHRP, when appropriate. We determine that the corrective actions noted above adequately address our determination with respect to Carle Clinic and are appropriate under the Carle Clinic FWA.

- (2) We determine that the Carle Clinic does not have a written procedure for ensuring verification from sources other than the principal investigator that there have been no material changes to research since the last IRB review, as required by HHS regulations at 45 CFR 46.103(b)(4)(ii).

Carle Clinic Required Action: Please provide us a written procedure for ensuring verification from sources other than the principal investigator that there have been no material changes to research since the last IRB review, as required by HHS regulations at 45 CFR 46.103(b)(4)(ii).

- (3) We determine that the Carle IRB is conducting expedited review in a way that is not consistent with the regulatory requirements at 45 CFR 46.108(b) and 45 CFR 46.110(b). HHS regulations at 45 CFR 46.108(b) require that the IRB review proposed research 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 nonscientific areas, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110. HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures for initial or continuing review to specific research categories published in the Federal Register at 63 FR 60364--60367 (see <http://www.dhhs.gov/ohrp/humansubjects/guidance/expedited98.htm>) when the research is determined to involve no more than minimal risk. As stated in HHS regulations at 45 CFR 46.110(b), expedited review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among the members of the IRB.

During our on-site interviews we learned that two individuals have been conducting expedited reviews on behalf of the Carle IRB even though these individuals are not experienced reviewers from among the members of the Carle IRB. According to the Carle IRB Membership Roster on file with our office, one of the individuals conducting expedited reviews on behalf of the Carle IRB was only appointed to the Carle IRB on February 20, 2009 and the other individual conducting expedited review on behalf of the Carle IRB was most recently appointed to the Carle IRB on August 27, 2009. We note further that it appears that one of the individuals conducting expedited review on behalf of the Carle IRB may have been conducting such expedited reviews even though he was not yet a Carle IRB member (this individual subsequently became a Carle IRB member on August 27, 2009). Moreover, we note that the expedited reviewers referenced above are not sufficiently knowledgeable about the expedited review research procedures and categories of research eligible for expedited review. In particular, in reviewing study 08426 “Illinois Emergency Department Asthma Surveillance Project (IEDASP),” we noted that while expedited review of this study was appropriate, the expedited reviewer approved this project under expedited review category #7. Because this study consisted of a survey plus a medical chart review, the study should have been reviewed and approved under expedited review categories #7 and #5. See also study 09108 “Barriers to Early Breast Cancer Detection.”

We also note that one of the IRB expedited reviewers, when processing a new study via the Carle expedited review procedure, was calculating IRB approval dates inappropriately. For example, study 09105 “Utilization of Video Capsule Endoscopy in a Community Hospital” received expedited review approval on June 1, 2009, although the IRB file reflects that the study was not reviewed and signed-off by the IRB designated expedited reviewer until June 3, 2009. Additionally, study 09107 “Evaluation of the Efficacy of Radiofrequency Ablation Using HALO Technique in Treatment of Barrett’s Esophagus with Dysplasia” received expedited review and approval on June 8, 2009 although the IRB file reflects that the study was not reviewed and signed-off by the IRB designated expedited reviewer until June 9, 2009.

Lastly, we note that one of the IRB expedited reviewers, when processing a minor modification via the Carle expedited review procedure, was calculating the modification approval date inappropriately. The study file for study 0731 “Development of Auditory Skills in Young Deaf Children With Cochlear Implants” reflects that the HSP staff received a protocol amendment on April 10, 2009 which was approved that same day even though the IRB chairperson did not review the amendments until April 13, 2009.

Given the above information, we determine that the Carle IRB is conducting expedited review in a way that is not consistent with the regulatory requirements at 45 CFR 46.108(b) and 45 CFR 46.110(b).

Carle Foundation Required Action: Please provide us with a corrective action plan that will ensure that the Carle IRB is conducting expedited review in a way that is consistent with the regulatory requirements at 45 CFR 46.108(b) and 45 CFR 46.110(b).

D. Questions and Concerns Regarding the Above-Referenced Research:

[Redacted]

E. Questions and Concerns Identified During the July 28 – July 30, 2009 Site Visit:

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

[Redacted]

(4) [Redacted]

(5) [Redacted]

(6) [Redacted]

(7) [Redacted]

(8) [Redacted]

F. Recommendations:

We recommend that Carle Foundation and the Carle Clinic implement appropriate training and education programs for investigators and research staff regarding the ethical principles and regulatory requirements related to the protection of human subjects. We believe that increased training and education would address many of the concerns we observed from our review of your reports and the site visit.

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Bruce Wellman, M.D. – Carle Clinic Association
James C. Leonard, M.D. – Carle Foundation Hospital
September 21, 2009

The remaining questions and concerns from our June 9, 2009 letter have been adequately addressed.

Please provide us with responses to the above determinations and questions and concerns by October 27, 2009. If you identify any noncompliance during your review of the above determinations and questions and concerns, please describe any corrective actions that have been or will be taken to address the noncompliance.

Please do not 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 Chairperson, Carle Foundation
Dr. N. Nadeem Ahmed, Current IRB Chairperson, 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, NCI
Dr. Lori Minasian, NCI
Ms. Joan Mauer, NCI
Dr. Angela Bowen, Western Institutional Review Board