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December 16, 2009

Bruce Wellman, M.D.  
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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 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:

Thank you for the October 27, 2009 Carle Foundation Hospital (Carle Foundation), November 9, 2009 and December 15, 2009 Carle Clinic Association (Carle Clinic) letters in response to our September 21, 2009 letter that included determinations, questions, and concerns. Based on the information submitted, we make the following determinations:

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

- (1) In our September 21, 2009 letter we required the following actions to be taken in response to our determination that the Carle Foundation and the Carle Clinic collectively failed to prepare and maintain adequate documentation of institutional review board (IRB) activities for the above-referenced research, in contravention of the Department of Health and Human Services HHS regulations at 45 CFR 46.115(a) and 46.115(b):

**Carle Foundation Corrective Action:** Carle Foundation was asked to provide us with a final report describing the study histories for the 156 closed Carle Clinic studies, which were to be submitted to the Carle Foundation IRB (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. We have received the requested final report. We determine that this final report, in addition to all previously identified corrective actions, adequately address our determination and is appropriate under the Carle Foundation FWA.

**Carle Clinic Corrective Action:** As requested, Carle Clinic provided us with a copy of a draft IRB Authorization Agreement (IAA) that will ultimately be executed by the Carle Clinic and an external IRB. We reviewed such document and have the following concerns:

- (a) Section 2(A)(i) entitled "Criteria for Which Studies Will be Reviewed by WIRB" – We note that according to this section of the IAA the "Institution [Carle Clinic] will determine if there are any local context issues that must be addressed by Institution, and Institution will refer such studies to proper Institution personnel rather than to IRB." Based on this language, it is not clear what will happen to the information relating to local context issues that is obtained by the Institution personnel. Please clarify.
- (b) IAA, Section 3 – We are concerned with the individual named as the Carle Clinic institution contact. Based on the institution contact responsibilities outlined in the draft IAA, i.e. to assure investigator and institutional compliance with IRB decisions, we believe that the institution contact should be a senior level employee who has the authority to assure investigator and Carle Clinic compliance with the IRB decisions. We do not believe that the individual named has such authority. As a result, we recommend that you identify a new institution contact.

**Carle Clinic Required Action:** Please clarify item (a) above.

- (2) In our September 21, 2009 letter we required the following actions to be taken in response to our determination that an investigator initiated protocol changes without IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii):

**Carle Foundation Corrective Action:** As requested, the Carle Foundation revised 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. We determine that this revision to the Carle IRB template for initial review and approval, in addition to all previously identified corrective actions, adequately addresses our determination and is appropriate under the Carle Foundation FWA.

**Carle Clinic Corrective Action:** The Carle Clinic was asked to: (a) revise the Carle Clinic Policy 5308 entitled “Reporting Safety Issues to IRB, FDA, Clinical Trial[s] Sponsors & the Human Protections Administrator,” or draft a new policy, to address those instances where an investigator prospectively anticipates making a change to an IRB-approved protocol; and (b) 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.

We acknowledge that the Carle Clinic has developed new Policy 5320 entitled “Planned Changes to IRB-Approved Research” to address those instances where an investigator prospectively anticipates making a change to an IRB-approved protocol. We also acknowledge that the Carle Clinic has or will implement the following actions to ensure 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:

- (a) The Carle Clinic Compliance Officer has presented training on this issue to Carle Clinic Research Associates on October 21, 2009;
- (b) The Carle Clinic Compliance Officer was scheduled to present a similar training to oncology physicians and nurses in November 2009;
- (c) Periodic audits will be conducted to confirm compliance with the newly implemented policy; and
- (d) This new policy and other requirements regarding changes to a protocol will be part of the Carle Clinic’s continuing education program for Cancer Center researchers.

We determine that these corrective actions, in addition to all previously identified corrective actions, adequately address our determination and are appropriate under the Carle Clinic FWA.

- (3) We previously 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. We asked the Carle Foundation to provide our office with the status of all of the studies noted in Attachment D of the Carle Foundation July 7, 2009 response that were **not** noted as having been closed by the Carle IRB or closed with the Carle IRB. This action was required because it was not clear from the information contained in Attachment D whether studies were 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 Foundation Corrective Action:** The Carle Foundation notified us that all of the studies that were **not** noted as having been closed by or with the Carle IRB are now closed. We determine that this status update, in addition to all previously identified corrective actions, adequately addresses our determination and is appropriate under the Carle Foundation FWA.

- (4) We previously determined that: (a) 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; and (b) 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). The Carle Clinic notified us that it was:
- (i) 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; and
  - (ii) 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.

Based on this information, we asked Carle Clinic to provide our office with documentation of all training that was completed by a noted August 31, 2009 completion date as well as a final outline/description of the Carle Clinic Research Audit Program.

**Carle Clinic Corrective Action:** We note that the Carle Clinic required cancer research investigators and key personnel to complete general training requirements by August 31, 2009; this date was ultimately extended to September 14, 2009. The general training covered a variety of topics including, but not limited to: the history of ethical principles; defining research with human subjects; basic IRB regulations and review process; informed consent; and conflicts of interest in research involving human subjects. We note that as of November 9, 2009 100% of Carle Clinic cancer research investigators and key personnel completed the mandatory training and 89% of Carle Clinic affiliate research investigators and key personnel completed the mandatory training. We note that

one Carle Clinic affiliate did not complete the general training requirement given that the affiliate has chosen not to renew its affiliation with Carle Clinic. We also acknowledge receipt of the Carle Clinic Research Audit Plan for the remainder of 2009 and 2010. We determine that these actions, in addition to all previously identified corrective actions, adequately address our determination and are appropriate under the Carle Clinic FWA

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

- (1) We previously determined 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). We asked the Carle Foundation to provide our office with quarterly reports regarding: (a) implementation of the corrective actions identified in this letter; and (b) the merged organizations' future plans for the protection of human subjects.

**Carle Foundation Corrective Action:** We acknowledge that the Carle Foundation will be providing our office with the first quarterly report on or before December 15, 2009.

- (2) We previously determined that the Carle Clinic did not have a written procedure for determining which projects need 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). As a result, Carle Clinic was asked to provide our office with a written procedure for determining which projects need 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 Corrective Action:** We acknowledge receipt of Carle Clinic Policy 5321 entitled "Verification of Material Changes to IRB-Approved Research from Sources Other Than the Principal Investigator." We determine that this corrective action adequately addresses our determination and is appropriate under the Carle Clinic FWA.

- (3) In our September 21, 2009 letter we determined that the Carle IRB conducted 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). As a result, Carle Foundation was asked to provide us with a corrective action plan that will ensure that the Carle IRB conducts expedited review in a way that is consistent with the regulatory requirements at 45 CFR 46.108(b) and 45 CFR 46.110(b).

**Carle Foundation Corrective Action:** We acknowledge that the Carle Foundation has implemented the following actions to address this determination:

- (a) Human Subjects Protection (HSP) specialists will initially review all IRB submissions using a newly developed Reviewer Worksheet and will make a provisional determination whether the submission qualifies for expedited review;
- (b) Using the same Reviewer Worksheet the HSP Director (who is a Carle IRB member) will review the provisional determination to determine if s/he concurs that the study qualifies for expedited review. If so, the HSP Director will conduct expedited review;
- (c) For the following six months, the IRB Chair will perform a concurrent expedited review to verify any conclusions and/or recommendations made by the HSP Director and to assess the competency of the HSP Director to conduct expedited reviews; and
- (d) All IRB members conducting expedited review will receive ongoing training on appropriate expedited review procedures/categories.

In addition, we note that the Carle Foundation has changed its procedure regarding the dating of IRB expedited review approval letters so that approval letters will not predate the date the review checklist is signed by the reviewer. We determine that these corrective actions adequately address our determination and are appropriate under the Carle Foundation FWA.

### **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) We determine that the Carle IRB meeting minutes do not adequately reflect discussion of controverted issues during IRB meetings, as required by 45 CFR 46.115(a)(2).

**Carle Foundation Corrective Action:** We acknowledge that the Carle Foundation has taken the following steps to address this determination:

- (a) Developed a reviewer worksheet for use by IRB members during their review of a study. The worksheet references the process for informed consent, recruitment of subjects, maintenance of the privacy of study subjects and confidentiality of study data;
- (b) Implemented a function through an electronic IRB system that permits staff to develop and use a template for IRB minutes which includes prompts relating to topics that must be discussed for each study reviewed;
- (c) Revised the policy "IRB Meeting Administration" (IRB 302) to specify that meeting minutes include the required elements; and
- (d) Implemented a plan that an internal auditor will monitor records of IRB minutes to confirm that the minutes contain the required elements.

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

- (2) In our September 21, 2009 letter the Carle Foundation was asked to clarify whether and how the Carle IRB considers the requirements of subpart B 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. We noted that there was no reference to the Carle IRB making the determinations required under subpart B for this research.

The Carle Foundation confirmed that neither the minutes nor the approval letter for study 080431 provided any reference to the Carle IRB making the determinations required under 45 CFR part 46, subpart B, in particular the determinations required by 45 CFR 46.204. Given this response, we determine that the Carle IRB did not make the required findings when reviewing the above-referenced research involving pregnant women.

**Carle Foundation Corrective Action:** We note that the Carle Foundation HSP Office has devised a pregnant women’s determination checklist to be used with any study that involves pregnant women.

**Carle Foundation Required Action:** We note that the Carle Foundation limited its response to the study referenced above although our original request was for Carle Foundation to clarify whether and how the Carle IRB considers the requirements of subpart B when reviewing all research involving pregnant women, fetuses, or neonates. Given this oversight, please audit all currently active research involving pregnant women, fetuses or neonates to determine whether the Carle IRB made the required findings under subpart B. Please provide our office with a report including the total number of currently active studies involving pregnant women, fetuses, or neonates that were reviewed and the number of those studies requiring re-review.

- (3) In our September 21, 2009 letter we raised a concern that the Carle IRB may not adequately document the findings required for waiver of the requirements for obtaining informed consent in accordance with HHS regulations at 45 CFR 46.116(d). This concern was raised after reviewing three separate studies.

We note that the Carle Foundation acknowledged the following:

- (a) IRB 04038 - The Carle IRB granted a waiver of informed consent as requested by the investigator, but IRB approval for the waiver of informed consent was not adequately documented by the IRB in either the minutes or the IRB approval letter;
- (b) IRB 08426 - There were no statements in the IRB meeting minutes which clarifies how the study met the criteria for a waiver of informed consent; and

- (c) Short and Long Term Effects of Lasix-Mannitol Infusion - The IRB minutes for this study did not document how the study met the criteria for a waiver of consent and the IRB approval letter simply stated that a full waiver of consent was approved.

Based on the above, we determine that for the above-referenced studies the Carle IRB did not find and document specific criteria when approving waiver of informed consent, as required by HHS regulations at 45 CFR 46.116(c) and (d).

**Carle Foundation Corrective Action:** We note that the Carle Foundation began utilizing a function in its electronic IRB system which allows IRB staff to develop a template for IRB meeting minutes which will include prompts relating to topics, e.g., request for a waiver of informed consent, which must be discussed for each study being reviewed. Thus, references to IRB approval of waiver of informed consent and of the basis for approval will be added to the minutes. In addition, revised approval letters will make clear whether any waivers of informed consent have or have not been granted. Lastly, we note that the Carle IRB will develop a form entitled Waiver or Alteration of Consent which will need to be completed by the investigator. We note that this form will have an “administrative use only” area which will allow the IRB Chair, or designee, to document how the study meets the criteria for waiver/alteration of consent. We determine that these corrective actions adequately address our determination and are appropriate under the Carle Foundation FWA.

**D. Carle Foundation and Carle Clinic Responses to Questions and Concerns Identified During the July 28 – July 30, 2009 Site Visit:**

- (1) In our September 21, 2009 letter we raised a concern regarding how the potential upcoming merger between Carle Foundation and Carle Clinic will affect the two entities’ proposed corrective action plans.

We note that Carle Clinic and Carle Foundation are scheduled to update us on the upcoming merger, as well as other issues, on or around December 15, 2009,. We note that the Carle Clinic decided to postpone reporting to us based on the belief that by December 15, 2009 there will be more information regarding the merger and how the merged organization will be structured. Notwithstanding this decision, we note that it is anticipated that the merger will result in one institution with a single FWA and that it is expected that Dr. Bruce Wellman, the current signatory official for Carle Clinic, will serve as the Signatory Official for the merged entity. We note further that Dr. Wellman’s position within the merged entity will be Chief Executive Officer of Carle Foundation and Carle Clinic, the second ranking executive in the enterprise, and that he will have responsibility and control over the resources dedicated to supporting human subjects research.

**Carle Foundation and Carle Clinic Required Action:** With the Carle Foundation's next quarterly progress report, please provide us with an update on the status of the upcoming merger between your two institutions and any proposed changes to your previously submitted corrective action plans.

- (2) In our September 21, 2009 letter we raised a concern regarding the breadth of Dr. Rowland's responsibilities in numerous research studies. We were concerned that his principal investigator (PI) responsibilities, in addition to his non-PI clinical care responsibilities, will not allow him to ensure that human subjects are adequately protected in each and every research study for which he is the PI. We noted that there may be circumstances in which if one individual has the responsibilities and duties of PI for an excessive number of complex clinical trials, this may lead to situations in which risks to subjects are not minimized. In addition, in that same letter we noted that the Carle Clinic had developed and began implementing a plan whereby some of Dr. Rowland's studies will be assigned to other PIs based on disease site. We also noted that according to an investigator who has recently been named a PI under this new plan, s/he has no oversight over the studies for which s/he has been named PI. Moreover, Dr. Rowland acknowledged that he does not believe that this plan will have any affect on his day-to-day operations or responsibilities as PI. In light of this information, it was not clear whether the Carle Clinic had taken adequate steps in assigning investigators to share Dr. Rowland's responsibilities. As a result, we asked the Carle Clinic to provide more information regarding how this concern is being addressed.

**Carle Foundation Corrective Action :** We note that the Carle Foundation developed a new policy requiring PIs to disclose the total number of studies (at all sites with all IRBs) for which s/he is serving as PI each time the PI submits a new study for IRB review/approval as well as at the time of continuing review. If the total number of studies for which an investigator is serving as PI exceeds 20, the investigator will be required to submit Appendix B: Research Resource Disclosure Form, discussing the resources and staffing for those studies. We note that the Carle Scientific Review Committee and the Carle IRB will then consider the information in their review of the study and determine whether any approval of the new study will be conditioned upon a change in the PI for the new study or a transfer of one of the investigator's existing studies to another PI. We determine that this corrective action adequately addresses our concern and is appropriate under the Carle Foundation FWA.

**Carle Clinic Corrective Action:** We note that the Carle Clinic has begun implementing a PI restructuring initiative under which the Carle Clinic has reassigned the responsibilities of one main PI to other medical oncology and radiation oncology physicians. Per your response, the PI restructuring initiative includes the following:

- (a) Identifying potential PIs by disease site;
- (b) Training newly identified PIs prior to assuming PI responsibilities;

- (c) Allocating studies on a go-forward basis utilizing a study intensity metric that measures the relative burden of managing a particular study based on subject status, study complexity and number of subjects in a particular study;
- (d) Reassigning current studies to different PIs;
- (e) Developing and/or redesigning reporting mechanisms;
- (f) Developing and maintaining adequate support structures that assist PIs with their responsibilities;
- (g) Assessing what impact this initiative will have on affiliate sites; and
- (h) Auditing and monitoring.

We determine that this PI restructuring initiative adequately addresses our question and concern and is appropriate under the Carle Clinic FWA.

The remaining questions and concerns from our September 21, 2009 letter have been adequately addressed.

Please provide us with responses to the above determinations and questions and concerns by January 13, 2010. 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  
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