DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 6, 2000

Harry P. Ward, M.D.
Chancellor
University of Arkansas for Medical Sciences
4301 Markham Street, Mail Slot 541
Little Rock, Arkansas 72205

Jonathan Bates, M.D.
President and Chief Executive Officer
Arkansas Children's Hospital
800 Marshall Street
Little Rock, Arkansas 72202

Tim Atkinson
Director of Research Support Center
Arkansas Children's Hospital Research Institute
1120 Marshall Street
Little Rock, Arkansas 72202

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1451

Research Project: POG 9440/CCG 4941 - National Wilms Tumor Study - 5: Therapeutic Trial and Biology Study
Project Number: 3942
Principal Investigator: David Becton, M.D.

Dear Dr. Ward, Dr. Bates, and Mr. Atkinson:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Ward's report of January 13, 2000 concerning the above referenced research project.

In reviewing the documents submitted with Dr. Ward's report, as well as additional documents provided by the complainant, OHRP notes the following regarding the above referenced research protocol:

(1) The Institutional Review Board (IRB) approved research protocol included the following stipulations:

(a) Tissue slides from the resected Wilms tumor, pathology reports, and National Wilms Tumor Study - 5 (NWTS #5) Pathology Checklists were to be mailed to the National Wilms Tumor Study Group (NWTSG) Pathology Center as soon as possible after surgery (see section 5.111).

(b) Stage II Wilms Tumor was to be defined as follows (see section 5.212):

"The tumor extends beyond the kidney, but was completely resected. There is regional extension of tumor (i.e., penetration of the renal capsule, . . .). The blood vessels outside the renal parenchyma, including those of the renal sinus, contain tumor."

(c) The treatment for stage I/focal Wilms tumor or diffuse anaplasia or for stage II/favorable histology Wilms tumor was nephrectomy and chemotherapy with a regimen designated as EE-4A which included (i) dactinomycin intravenously within 5 days post nephrectomy, and then at weeks 3, 6, 9, 12, and 18; and (ii) vincristine intravenously at day 7 post nephrectomy, then weekly for 10 doses, and with dactinomycin at weeks 12, 15, and 18 (see sections 6.12 and 6.13).

(d) The treatment for stage II/focal anaplasia on histology was nephrectomy, abdominal irradiation, and chemotherapy with a regimen designated as DD-4A which included (i) dactinomycin intravenously within 5 days post nephrectomy, and then at weeks 6, 12, 18, and 24; vincristine intravenously at day 7 post nephrectomy, then weekly for 10 doses, and with dactinomycin or doxorubicin at weeks 12, 15, 18, 21, and 24; and (iii) doxorubicin intravenously at weeks 3, 9, 15, and 21 (see section 6.14).

(e) Investigators were to call the NWTSG Data and Statistical Center (DSC) to report changes in stage, histology, or treatment (see section 9.1)

(2) On May 4, 1997, subject 50667 (TS) underwent left radical nephrectomy for a renal mass.

(a) An Operative Report, signed by Dr. Samuel Smith, reported that subject 50667's tumor extended into the renal vein.

(b) A Pathology Report (97:SU1284), dated May 6, 1997, and signed by Dr. Roby Thomas, a pathologist at Arkansas Children's Hospital, reported that (i) subject 50667 had a triphasic nephroblastoma (Wilms tumor) with focal anaplasia; (ii) the anaplastic component was present in approximately 5-10 % of the examined tumor; and (iii) the tumor extended through the renal capsule to involve perinephric tissue.

(c) The Operative Report and Pathology Report findings indicate that subject 50667 clearly had stage II/focal anaplasia Wilms tumor.

(3) An informed consent document signed and dated on May 8, 1997, by the mother of subject 50667 and entitled "NWTS #5: STAGE I/FAVORABLE HISTOLOGY (AGE AT DIAGNOSIS > 24 MONTHS AND/OR TUMOR SPECIMEN WEIGHT > 500 GRAMS), STAGE I/FOCAL OR DIFFUSE ANAPLASIA, STAGE II/FAVORABLE HISTOLOGY" indicates that subject 50667 was placed on regimen EE-4A by Dr. Becton.

(4) A NWTS-5 Telephone Registration form for subject 50667 indicates the following:

(a) The subject was enrolled in the NWTS-5 clinical trial and biology study on May 9, 1997, with Dr. Becton as the treating physician

(b) The subject's tumor was initially designated as stage I, with focal anaplasia on histology (unfavorable histology).

(c) The subject was placed on regimen EE-4A (chemotherapy with dactinomycin and vincristine, without abdominal irradiation).

(5) In a May 12, 1997 facsimile memorandum to Dr. Becton, the National Wilms Tumor Study Group stated the following:

"As of this morning slides of patient 50667 have not been received by the NWTSG pathologist, Bruce Beckwith, M.D., in Loma Linda, CA. While it is rare that an institutional pathologist misses the diagnosis of anaplasia, the consequences of such an event are significant for the patient, especially if the anaplasia is detected too late to influence the child's outcome.

"On behalf of the NWTSG Committee we request that you contact the pathologist responsible for this case and urge her or him to send the slides to Dr. Beckwith immediately."

(6) The January 6, 2000 investigation report from Dr. Thomas Wells states that in June or July 1997, Dr. Becton realized that subject 50667 had been placed on the wrong arm of

the NWTS-5 study because he had stage II disease with focal anaplasia. Subject 50667 remained on regimen EE-4A following this realization.

(7) In a September 16, 1997 letter to Dr. Paul Haut, a physician in Chicago who was going to assume responsibility for follow-up monitoring of subject 50667 following completion of his chemotherapy regimen, Dr. Becton stated the following:

> "As you can see, [subject 50667] was diagnosed in May of this year with a large left renal mass which appeared to be a Wilm's tumor with favorable histology. He initially was registered as a stage 1 but on further review his tumor capsule was invaded and he was changed to a stage II favorable histology. This made no change in his protocol therapy. He received 18 weeks of outpatient therapy with vincristine and actinomycin-D. . . . He will be scheduled for his end of therapy evaluation in approximately three weeks. . . . Per the protocol he does not require chest CT based on his negative CT at initial diagnosis."

(8) In an October 23, 1997 letter to Dr. Roby Thomas, Dr. Beckwith stated the following:

> "Thank you for this case which arrived by courier delivery on October 22, though the surgery was performed last May. I confirm your diagnosis of **focal anaplasia** for this Wilms tumor. . . .
>
> "This tumor is not stage 1. It fills a large branch, or even the main trunk, of renal vein in A5. It is also extensive in the renal sinus in A7 . . . ." [emphasis in original].

(9) On March 25, 1999, subject 50667 died from progression of advanced stage Wilms tumor.

OHRP Finding Regarding NWTS-5

Based on its evaluation of the above referenced documents, OHRP makes the following determination regarding the above referenced research project:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) and 46.103(b)(5), as well as the University of Arkansas for Medical Sciences (UAMS) MPA, require that unanticipated problems involving risks to subjects or others be promptly reported to appropriate institutional officials, the IRB, OHRP, and the head of the sponsoring Federal department or agency.

OHRP finds that (a) the failure of the principal investigator to appropriately stage the subject 50667's Wilms tumor as a Stage II tumor with focal anaplasia and assign the subject to regimen DD-4A represented a serious unanticipated problem involving risk to

the subject; and (b) upon recognizing the error in staging in June or July 1997 (per your report), the investigator failed to promptly report this problem to appropriate institutional officials, the IRB, OHRP, and the sponsoring Federal department or agency.

Action 1 - Required: By December 4, 2000, the UAMS and Arkansas Children's Hospital (ACH) must submit to OHRP a satisfactory corrective action plan to ensure that all unanticipated problems involving risks to subjects or others are promptly reported in accordance with the requirements of HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Additional OHRP Concerns and Questions Regarding NWTS-5

(2) HHS regulations at 45 CFR 46.111(a)(1) require that the in order to approve research the IRB must determine that risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk. It appears the following deviations from the IRB-approved protocol by the principal investigator, as well as other actions following the deviations, failed to ensure that risks to subject 50667 were minimized:

(a) Failure of the investigator either to review the above referenced Operative Report and Pathology Report related to subject 50667, or to recognize that the data in these reports clearly indicated that the subject had stage II Wilms tumor with focal anaplasia, resulting in the subject being placed on a chemotherapy regimen that was appropriate for stage I Wilms tumor with focal anaplasia, but not for a stage II tumor with focal anaplasia.

(b) Failure of the investigator to ensure that the Pathology Report and tissue slides from subject 50667's tumor were promptly submitted to the NWTSG Pathology Center for review to confirm the diagnosis and tumor histology. Despite a written request from the NWTSG Pathology Center dated May 12, 1997, to Dr. Becton to have the pathologist submit these materials immediately, the NWTSG Pathology Center did not receive them until October 22, 1997, after subject 50667's chemotherapy regimen had been completed.

(c) Failure of the investigator to promptly report to the NWTSG Data and Statistical Center a change in the stage of subject 50667 in June or July 1997 when he reportedly recognized the error in staging.

(d) When transferring subject 50667 to another physician, Dr. Haut, in September 1997 for continued monitoring and follow-up under the protocol, the investigator failed to report that the prior errors in staging of the subject's tumor and in

classifying the subject's tumor histology resulted in inappropriate treatment assignment under the IRB-approved protocol.

Please respond in detail.

(3) It appears possible that the apparent deviations cited above may have contributed to the premature death of subject 50667. Please respond.

(4) Your report indicates that Dr. Becton realized in June or July 1997 that subject 50667 should have been stage II with focal anaplasia and had been placed on the wrong arm of the study. However, in his September 16, 1997 letter to Dr. Haut, Dr. Becton stated that while there was an initial error in staging subject 50667's tumor, the tumor had favorable histology, and thus the staging error had no effect on his protocol therapy. OHRP is unable to reconcile the information provided in your report and Dr. Becton's September 16, 1997 letter. Please respond.

(5) OHRP recognizes that management decisions regarding patients with Wilms tumors can be complex and require multi-disciplinary team involvement. Please clarify whether Dr. Becton consulted with other appropriate specialists or experts at either UAMS or ACH or within the NWTSG in June or July 1997 when he recognized the error in staging subject 50667's disease. If so, please provide all documents relevant to such consultations.

(6) Given the nature of the events related the conduct of NWTS-5 at UAMS and ACH, OHRP is concerned that the corrective actions proposed in your report for Dr. Becton may not be sufficient. In particular, it appears that it may be appropriate for the IRB to require additional monitoring and oversight of Dr. Becton's research activities. Please respond.

(7) Your report indicated that all studies being conducted by Dr. Becton were to be audited. Please provide OHRP with copies of all reports and documents related to these audits.

(8) Please describe the training provided to Dr. Becton and other NWTS staff at your institutions.

OHRP Findings, Concerns, and Guidance Regarding UAMS and ACH Systemic Protections for Human Subjects

(9) OHRP finds that the UAMS does not have adequate written IRB policies and procedures for the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB follows for conducting its continuing review of research.

(b) The procedures which the IRB follows for reporting its findings and actions regarding initial and continuing review to the institution.

(c) The procedures which the IRB follows for determining which projects require review more often than annually.

(d) The procedures which the IRB follows for determining which projects need verification from sources other than the investigators that no material changes have occurred since the previous IRB review.

(e) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the head of any supporting Federal Department or Agency, and OHRP of each of the following events:

(i) Any unanticipated problems involving risks to subjects or others.

(ii) Any serious or continuing noncompliance with the requirements of 45 CFR Part 46, or the requirements or determinations of the IRB.

(iii) Any suspension or termination of IRB approval of research.

Action 2 - Required: By December 4, 2000, the UAMS must submit revised written IRB policies and procedures that describe the operational details for the procedures followed by the IRB for each of the above activities. To assist the UAMS in revising its IRB policies and procedures please see the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(10) HHS regulations at 45 CFR 46.115(a)(2) require, among other things, that minutes of IRB meetings be in sufficient detail to show the vote on each IRB action including the number of members voting for, against, and abstaining and a written summary of the discussion of controverted issues and their resolution. OHRP finds that the minutes of UAMS IRB meetings that were provided with your report failed to document the number of members voting for, against, and abstaining on each IRB action. OHRP notes that recording votes as unanimous is not sufficient. Furthermore, OHRP is concerned that the minutes rarely reflect discussions of controverted issues.

Action 3 - Required: By December 4, 2000, the UAMS must submit a satisfactory corrective action plan to ensure that votes on each IRB action and all discussions of controverted issues are recorded in the minutes of IRB meetings in accordance with HHS regulations at 45 CFR 46.115(a)(2). In order to document the continued existence of a

quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(11) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

OHRP is concerned that continuing review of research by the UAMS IRB regularly fails to satisfy these requirements. In specific, it appears that the IRB receives insufficient information from investigators in continuing review reports, and separate substantive deliberations and votes do not occur for each protocol undergoing continuing review by the convened IRB. Please respond.

(12) Based upon its review of the minutes of IRB meetings, OHRP is concerned that on occasion the UAMS IRB approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure. Please respond.

(13) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, the approval period must begin on the date the protocol was reviewed by the convened IRB, not on the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. (Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.)

OHRP is concerned that on occasion the UAMS IRB failed to conduct continuing review of research at least once per year. Please respond.

Please provide your response to the above questions and concerns so that OHRP receives it no later than December 4, 2000.

OHRP appreciates the continued commitment of your institutions to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

Enclosures: (1) Guidance for Formulating Written IRB Policies and Procedures
(2) OPRR Reports 95-01

cc: Dr. Fred H. Faas, Chair, IRB, UAMS
Dr. David Becton, UAMS
Ms. Joan Mauer, CTEP, NCI, NIH
Dr. Malcolm Smith, CTEP, NCI, NIH

cc's continued:

Commissioner, FDA
Dr. David Lepay, FDA
Dr. James McCormack, FDA
Dr. John Mather, ORCA, Department of Veterans Affairs
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Katherine Duncan, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Clifford C. Scharke, OHRP
Mr. Barry Bowman, OHRP