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June 14, 2001

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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. Wilson and Dr. Bates:

The Office for Human Research Protections (OHRP) has reviewed your January 12, March 1, and June 1, 2001 reports regarding the above referenced research and your institutions' systemic protections for human subjects that were submitted in response to OHRP's November 6, 2000 letter.

OHRP Findings Regarding POG 9440/CCG 4941 - National Wilms Tumor Study - 5: Therapeutic Trial and Biology Study

In reviewing all documents previously submitted by the University of Arkansas for Medical Sciences (UAMS) and Arkansas Children's Hospital (ACH), as well as additional documents provided by the complainant, OHRP notes the following regarding the above referenced research protocol:

(1) The research protocol approved by the UAMS Institutional Review Board (IRB) 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) and no more than 4 weeks after the date of surgery (see section 9.27).

(b) Stage II Wilms Tumor was 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 presence of anaplasia was the only criterion for "unfavorable" histology in a Wilms Tumor (see section 5.131).

(d) 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).

(e) 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).

(f) Investigators were required to report changes in stage, histology, or treatment to the NWTSG Data and Statistical Center (see section 9.1). Furthermore, all patients were to continue on-study in order to maintain follow-up unless pathology review caused a change in diagnosis to mesoblastic nephroma or non-Wilms. In such cases, the subject's status was to be changed to "REGISTERED ONLY" (see section 9.1112).

(2) On May 4, 1997, subject 50667 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 ACH, 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 indicated 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 indicated 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.

(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." [italics added for emphasis]

(6) The January 6, 2000 investigation report from Dr. Thomas Wells stated 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." [italics added for emphasis]

(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 of progression of advanced stage Wilms tumor.

(10) Your January 12, 2001 report stated the following:

> (a) Observations in (1)-(9) above were correct.
>
> (b) At the time of subject 50667's diagnosis, Dr. Becton "thought there was no focal anaplasia. [He] did not read the pathology report until several weeks later."
>
> (c) Dr. Becton discovered in June or July 1997 that his understanding of the histology of subject 50667's tumor was incorrect.

(d) "Misclassification [of subject 50667's tumor] and assignment [of subject 50667] to treatment EE-4A rather than DD-4A represents a protocol violation. This protocol violation was significant and when discovered should have been reported to appropriate institutional officials, the IRB, the NWTSG, and OHRP."

(e) "Regardless of why the slides [for subject 50667] were not sent to the NWTS Pathology Center, it is clear that currently there is no process to ensure that the tissue slides and pathology report are sent to the study sponsor. Similarly, there appears to be no formal process for Dr. Becton to verify that the tissue slides and pathology reports have been sent when required by the research protocol."

(f) "It is possible that the assignment of [subject 50667] to the EE-4A treatment regimen rather than the DD-4A regimen may have contributed to the apparent failure of chemotherapy to eliminate his tumor. However, as Dr. Becton points out, it is possible that microscopic spread of the tumor to the liver has already occurred at the time of initial diagnosis."

(g) "Nothing in [subject 50667's] medical record documents indicates any consultation [with other appropriate specialists or experts at either UAMS or ACH or within NWTSG] at the time the correct histological classification [or subject 50677's tumor] was discovered."

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

(1) In its November 6, 2000 letter to UAMS and ACH, OHRP found that (a) the failure of the principal investigator to appropriately stage 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 UAMS's January 13, 2000 report), the investigator failed to promptly report this problem to appropriate institutional officials, the IRB, OHRP, and the sponsoring Federal department or agency, as required by 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.

Corrective Actions: OHRP finds that UAMS and ACH have developed and implemented satisfactory corrective action plans to ensure that all unanticipated problems involving risks to subjects or others are promptly reported to appropriate institutional officials, the IRB, OHRP, and the sponsoring Federal department or agency, as required by OHRP in its November 6, 2000 letter. In particular, OHRP notes that following:

(a) A letter from the Chancellor of UAMS and the President of ACH was sent to all investigators detailing their reporting responsibilities regarding unanticipated problems involving risks to subjects or others.

(b) UAMS and ACH conducted a series of educational forums for investigators regarding investigator-reporting responsibilities.

(c) The UAMS IRB's handbook for investigators has been revised to reinforce investigators' responsibility for reporting unanticipated problems involving risks to subjects or others.

(d) UAMS and ACH have implemented mandatory education for all investigators conducting human subject research.

(e) UAMS has established a Research Compliance Office which will conduct regulatory audits of human subject research protocols.

(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. Furthermore, in accordance with HHS regulations at 45 CFR 46.103(b)(4), an investigator may not make changes to the approved research procedures without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject.

Based upon the following observations, OHRP finds that the principal investigator failed to ensure that risks to subject 50667 (and perhaps other subjects) were minimized:

(a) The principal investigator failed to ensure that the IRB-approved research design was followed. In specific, the principal investigator failed to ensure that (i) the pathology report and representative slides of subject 50667's tumor were mailed to the NWTSG Pathology Center within 4 weeks after the subject's surgery (instead, these materials were not sent to the NWTSG Pathology Center until more than 5 months after the subject's surgery, by which time subject 50667 had already completed protocol regimen EE-4A); and (ii) changes in subject 50667's tumor stage and/or histology were reported to NWTSG Data and Statistical Center.

(b) The principal investigator failed to review the pathology report related to subject 50667 until at least several weeks after the subject was enrolled in the protocol.

(c) The principal investigator failed to establish and follow procedures for ensuring that (i) final operative and pathology reports were reviewed promptly for all subjects who were enrolled in clinical research protocols; and (ii) tissue slides and pathology reports were sent to the study sponsor.

(d) As a result of (b) and (c) above, the principal investigator failed to classify subject 50667's Wilms tumor as being stage II with focal anaplasia, resulting in the subject being placed on a less aggressive treatment regimen that was not appropriate for stage II Wilms tumor with focal anaplasia under the IRB-approved protocol.

(3) HHS regulations at 45 CFR 46.116(b)(5) require that, when appropriate, informed consent should include a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

OHRP finds that:

(a) The IRB-approved informed consent document signed by the mother of subject 50667 included the element of informed consent stipulated by HHS regulations at 45 CFR 46.116(b)(5).

(b) The principal investigator's discovery several weeks after the date of subject 50667's enrollment in the research that he had misclassified the subject's tumor represented a significant new finding developed during the course of the research that may have related to the subject's (or his parents') willingness to continue participation.

(c) There is no documentation in the clinical or research records that the principal investigator informed subject 50667's parents about the misclassification of the subject's tumor and inappropriate treatment group assignment.

(4) OHRP concurs with the statement in your January 13, 2001 report that it is possible that the assignment of subject 50667 to the EE-4A treatment regimen rather than the DD-4A regimen may have contributed to the apparent failure of chemotherapy to eliminate his tumor.

(5) UAMS' January 13, 2000 report indicated 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 UAMS' January 13, 2000 report and Dr. Becton's September 16, 1997 letter.

Corrective Actions: OHRP finds that UAMS and ACH have developed and implemented satisfactory corrective action plans to address findings (2)-(5) above. In particular, OHRP notes that following:

(a) The UAMS IRB and administration suspended all of Dr. Becton's research studies on November 9, 2000. The suspension was rescinded by UAMS on May 9, 2001 after all of Dr. Becton's human subject research activities were audited and corrective actions required by UAMS (see below) were implemented.

(b) The UAMS IRB required that Dr. Becton have all continuing review reports reviewed by the Research Compliance Office before submission to the IRB.

(c) Dr. Becton was required to develop a procedure to ensure that final operative and pathology reports are reviewed promptly for all patients who are enrolled in his clinical research protocols.

(d) Dr. Becton and his research staff underwent appropriate training by the Research Compliance Office regarding investigator reporting responsibilities and the continuing review process.

(e) Dr. Becton was required to develop a procedure to ensure that the NWTSG Pathology Center receives that pathology specimens and reports in accordance with protocol instructions and that such would be documented in subjects' study files.

(f) Following the rescinding of the suspension of Dr. Becton's research studies, the Research Compliance Office required Dr. Becton to verify randomization of subjects with a second faculty member from the ACH Hematology Oncology Division for 12 months.

(g) Every 6 months, the Research and Compliance Office will conduct an audit of the randomization process, informed consent, and IRB documentation for Dr. Becton's studies and the implementation of the pathology specimen processing procedures used by Dr. Becton and his research personnel. Following each six-month review, the Research Compliance Office will report the findings to the convened UAMS IRB and to the Vice Chancellor for Academic Affairs and Sponsored Research. Based upon the results of the audits, a plan for continued monitoring and oversight of Dr. Becton will be developed.

OHRP Findings Regarding Systemic Protections for Human Subjects at UAMS and ACH

OHRP makes the following determinations regarding systemic protections for human subjects at UAMS and ACH:

(6) OHRP finds that UAMS has developed written IRB policies and procedures that adequately describe all activities required by HHS regulations at 45 CFR 46.103(b)(4) and (5), as required by OHRP in its November 6, 2000 letter.

(7) OHRP finds that the UAMS IRB has revised its procedures to ensure that minutes of IRB meetings include (a) documentation of the number of members voting for, against, and abstaining on each IRB action, and (b) a summary of the discussion of controverted issues and their resolution, as required by HHS regulations at 45 CFR 46.115(a)(2).

(8) OHRP finds that UAMS and ACH have developed and implemented satisfactory corrective action plans to address the additional concerns regarding the systemic protections for human subjects at UAMS and ACH that were raised by OHRP in its November 6, 2000 letter. In particular, OHRP notes that following:

(a) The UAMS procedures for conducting continuing review have been improved to ensure that the review is substantive, meaningful, and timely.

(b) UAMS has expanded the number of IRBs from one to three, and increased the frequency of IRB meetings from monthly to weekly, thus reducing the volume of research overseen by a given IRB.

(c) UAMS has hired additional staff to support its IRBs.

(d) UAMS has expanded the IRB office space by more than two-fold.

(e) UAMS has revised and expanded its written IRB policies and procedures.

(f) UAMS has established a compliance program that includes (i) investigations of self-reported noncompliance by investigators and noncompliance discovered by the IRB or reported to the Research Compliance Office; and (ii) random and targeted compliance audits.

(g) UAMS and ACH have established mandatory education programs for investigators and key study personnel involved in the conduct of human subject research.

As a result of the above referenced corrective actions taken by UAMS and ACH, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter these determinations.

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

cc: Dr. Fred H. Faas, Chair, IRB, UAMS
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