DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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February 13, 2003

Ms. Judith K. Argon
Vice President, Research Administration
The Children's Hospital of Philadelphia
The Joseph Stokes, Jr., Research Institute
Abramson Pediatric Research Center
3516 Civic Center Blvd.
Philadelphia, PA 19104

RE: Human Research Protections Under Federalwide Assurance (FWA) FWA-0459 and Multiple Project Assurance (MPA) M-1388

Journal Article: Sutton LN, et al. Improvement in Hindbrain Herniation Demonstrated by Serial Fetal Magnetic Resonance Imaging Following Fetal Surgery for Myelomeningocele. JAMA. 1999:1826-1831

Dear Ms. Argon:

The Office for Human Research Protections (OHRP) has reviewed the Children's Hospital of Philadelphia's (CHOP) August 11, 2000 and June 28, 2002 reports regarding the above-referenced research, that were submitted in response to OHRP's letters of May 25, 2000 and January 30, 2002.

Based upon its review, OHRP makes the following determinations regarding this research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b) and 46.109(a) require that an institutional review board (IRB) must review and approve all non-exempt human subject research covered by an Assurance with OHRP.

HHS regulations at 45 CFR 46.102(d) define "research" as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. HHS regulations at 45 CFR 46.102(f) define a "human subject" as a living individual about whom an investigator conducting research obtains (i) data through intervention or interaction with the individual; or (ii) identifiable private information. Activities

which meet these definitions constitute human subject research under the HHS regulations for the protection of human subjects. Under CHOP's OHRP-approved Assurance, CHOP has agreed to comply with the requirements of the HHS regulations for all human subject research regardless of sponsorship.

OHRP finds that the above-referenced publication, as well as other activities uncovered in the course of CHOP's investigation regarding this matter, involved non-exempt human subject research that was conducted without being reviewed and approved by CHOP's IRB. In particular, OHRP notes the following:

(a) Based upon statements in the above-referenced journal article and CHOP's letters and reports of August 11, 2000 and June 28, 2002, it appears that Dr. Leslie Sutton and colleagues systematically collected information, both retrospectively and prospectively, on infants who underwent fetal myelomeningocele repair with such information designed to develop or contribute to generalizable knowledge. CHOP's letter of August 11, 2000 stated that the retrospective chart review evaluating the outcome of infants who had undergone fetal myelomeningocele surgery that resulted in the above-referenced journal article "should have been submitted for IRB review but was not submitted."

(b) CHOP's letter of June 28, 2002 acknowledged that the above-referenced journal article's description of the assignment of grades to MRIs to objectively evaluate the posterior fossa abnormality "should have been submitted to the IRB for review; it was not..."

(c) According to CHOP's letter of June 28, 2002, Dr. Sutton, first author of the above-referenced journal article and Division Chief of Neurosurgery at CHOP, "independently started an electronic data collection, which is on an Excel spreadsheet, in May 1999, approximately when he was working on the Journal Article." With regard to this spreadsheet, OHRP notes the following:

(i) CHOP asserts that this spreadsheet was used primarily for the clinical management of patients, but CHOP acknowledged that "the use of this collection of existing data to prepare the [above-referenced] Journal Article was research and should have been reviewed and approved by the IRB."

(ii) In preparing its response to OHRP's letter of January 30, 2002, CHOP learned that data from Dr. Sutton's spreadsheet had been used in the preparation of an unpublished abstract for a meeting held in December 2001, and was also being used <u>prospectively</u>, in the preparation of a new manuscript, although IRB review and approval had not been performed.

(d) In response to OHRP's request of January 30, 2002, CHOP compiled publications, abstracts and presentations by CHOP personnel involving the procedures described in the above-referenced journal article, made an independent judgement about whether it involved human subject research as defined by HHS regulations at 45 CFR 46.102, and attempted to match those projects defined as research with IRB records. According to CHOP's letter of June 28, 2002, CHOP concluded that two of these abstracts, consisting of retrospective chart review, involved research that lacked IRB approval.

(e) In addition, CHOP's letter of June 28, 2002 reported that a review of publications and published abstracts by CHOP's Center for Fetal Diagnosis and Treatment (the "Center") staff from 1997 through March 2002 "identified at least seven other materials that reported, or may have reported, on research that did not have IRB review," all of which involved retrospective chart review. CHOP notes that two of these seven publications involved the relative merits of MRI and ultrasound in prenatal diagnosis; however, "...there was no IRB approved protocol to conduct this comparison of existing [ultrasound] and MRI images."

Corrective actions: OHRP acknowledges that CHOP has conducted an investigation of the concerns outlined in OHRP's letters of May 25, 2000 and January 30, 2002, which included findings detailed above. In its letter to OHRP dated June 28, 2002, CHOP outlined its corrective action plan which included the following actions:

(i) Letters from CHOP president and CEO to Center leadership and specific Center staff, expressing concern about the failure to obtain IRB review where required, making clear that further instances of non-compliance will result in more severe steps.

(ii) Education and monitoring of Center staff, including a special monitoring program for at least the next three years in which all professional staff will be required to complete a semi-annual report on past, current and planned data collection and analysis, publication and presentation activities, along with a certification that no research activities are being conducted without IRB review.

(iii) A special educational review session with the entire professional membership of the Department of Radiology to review IRB regulations related to the conduct of clinical research, including issues related to the use of existing records, and a review of all existing MRI protocols to ensure that analyses and resulting images will be limited exclusively to the purpose of the IRB-approved protocols.

(iv) Development of guidance for the CHOP research community on the collection of clinical data and circumstances in which clinicians should submit plans for prospective data collection to the IRB for a determination on whether research is involved.

(v) Revision of IRB forms and procedures for use of existing data, including retrospective chart reviews, including the requirement that investigators submit to the IRB additional information on the sources of data, proposed consent processes, data and privacy security plans, and the proposed data collection tool.

(vi) Revision of IRB policies, including CHOP's Guidelines for Use of Human Subjects.

(vii) Institutional education on the use of human subjects in research, including revision of CHOP's human research training program to include additional material on the definition of research and the differences between prospective and retrospective uses of data.

(2) HHS regulations at 45 CFR 46.116 and 46.117 stipulate that no investigator may involve a human subject in research unless the investigator has obtained and documented the legally effective informed consent of the subject, except under limited circumstances approved by the IRB. OHRP finds that the investigators involved research related to the above-referenced journal article initiated human subject research, as outlined in item (1) above, without meeting this requirement. Specifically, OHRP notes that Dr. Sutton used a spreadsheet containing clinical data on individuals who received prenatal surgery for myelomeningocele (see item (1)(c)(ii) above) for the preparation of a manuscript, without obtaining and documenting legally effective informed consent of the subjects or obtaining IRB approval of a waiver of these requirements. In addition, CHOP acknowledged in its letter of June 28, 2002 to OHRP that the informed consent document for Dr. Adzick's protocol entitled "Physical and Neuro Developmental Follow up of Children with In Utero Repair of Spina Bifida ("follow up study") did not specify that existing data from CHOP's medical records would be analyzed as part of the research protocol.

Corrective action: OHRP acknowledges the corrective actions by CHOP outlined in item (1) above to ensure that investigators are aware of regulatory requirements for IRB review of research and for obtaining and documenting informed consent of participants. With respect to Dr. Sutton's use of data from his spreadsheet for the preparation of a new manuscript, OHRP notes that CHOP required Dr. Sutton to submit a request for IRB approval of this activity, and that each of the families participating in this study was contacted and asked for consent to use these data for the purposes of research analyses. Regarding Dr. Adzick's follow up study, OHRP notes that the informed consent document has been modified to expressly permit the access to existing data.

OHRP finds that the corrective actions listed above adequately address OHRP's findings and are appropriate under CHOP's FWA and MPA. As a result, OHRP is closing the case and 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 this determinations.

At this time, OHRP provides the following observations and guidance:

(3) OHRP acknowledges CHOP's view that the fetal surgery procedures described in the above-referenced journal article were innovative therapies, the performance of which did not constitute research, and that "...the distinction between innovative care and research may be especially complex to apply to surgical intervention" because "[unlike] new drugs or devices, surgical innovation is not regulated by the FDA. In many cases of surgical innovation...there may not be a clearly articulated hypothesis before performing the procedure, and there may not be a systematic, planned investigation nor an expectation to derive generalizable results" (CHOP letter to OHRP dated June 28, 2002).

OHRP recognizes that the distinction between research and clinical practice is often blurred and the application of innovative therapy in the management of patients does not necessarily make such activities research. The Belmont Report states the following regarding the boundaries between research and clinical practice:

> When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective.

As of June 28, 2002, 51 cases of fetal surgery for myelomeningocele had been performed at CHOP. CHOP stated in its June 28, 2002 letter that the CHOP IRB approved a protocol for a randomized, controlled trial of fetal surgery for myelomenigocele, as one of three sites for the NIH-funded Management of Myelomeningocele Study (MOMS). According to CHOP's June 28, 2002 letter, once the study begins, all three sites will offer fetal therapy for myelomeningocele only as part of the randomized controlled trial; the trial was set to commence in the fall of 2002. OHRP notes that in a November 13, 2000 letter to Dr. Adzick, the CHOP IRB provided contingent approval of this study, including the following recommendation:

> "...Now that it is recognized that a controlled trial is necessary to determine the safety and efficacy of fetal myelomeningocele repair, the continued performance of the procedure in an uncontrolled fashion may be difficult to justify. Although the committee did not support a blanket recommendation that all further fetal surgery for this indication stop until the trial begins, it felt that you should be aware of its concerns....You should advise the mother and father (if available) that this research trial is currently under consideration, so that they are aware of the existing uncertainty of this procedure" (CHOP letter to OHRP of June 28, 2002, Exhibit 4).

If it has not already done so, CHOP may wish to consider establishing a committee to independently review proposed innovative therapeutic interventions from across the institution, in order to determine in advance whether a particular intervention involves human subject research and should be conducted under an IRB-approved protocol.

OHRP appreciates the continued commitment of CHOP to the protections of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Division of Compliance Oversight

cc: Ms. Judith K. Argon, Vice President, Research Administration, CHOP
Ms. Lynn A. Bevan, Administrative Director, Research Regulatory Affairs, CHOP
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