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: 240-453-8298
FAX: 240-453-6909
E-mail: pmcneilly@osophs.dhhs.gov

August 26, 2005

Robert S. Chang, Ph.D.
Vice President for Research
University of South Florida
4202 E. Fowler Avenue, ADM 200
Tampa, FL 33620-5920

Gary A. Carnes
Chief Executive Officer
All Children's Health System, Inc.
801 Sixth Street South
St. Petersburg, FL 33701

RE: Human Research Subject Protections Under Federalwide Assurances FWA-1669 and FWA-997

Research Activity: **Very High Dose Recombinant Erythropoietin (rEpo) as a Neuroprotectant for Neonates at Risk for Periventricular-Intraventricular Hemorrhage (PV-IVH)**
Investigators: **Stacey M. Levitt, Darlene A. Calhoun, Bruce Martin, Samuel E. Fox, and Robert D. Christensen**

Dear Dr. Phillips and Mr. Carnes:

The Office for Human Research Protections (OHRP) has reviewed the University of South Florida's (USF) and All Children's Health System, Inc.'s (ACH) May 29, 2003 report in response to OHRP's April 25, 2003 and April 28, 2003 letters regarding the above-referenced research.

In reviewing the report submitted by USF and ACH, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 require that in order to approve research, an institutional review board (IRB) shall

determine that certain requirements are satisfied, including that (i) risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) risks to subjects are reasonable in relation to anticipated benefits and the importance of the knowledge that may reasonably be expected to result.

OHRP notes the following:

(a) The IRB-approved protocol states the following:

(i) "No clinical data are available on the neuroprotective and neurotrophic effects of rEpo in human neonates."

(ii) "Similarly, in adults no data on the application of high-dose rEpo as a neuroprotective agent are available."

(iii) "Before any clinical inference can be made about the feasibility of rEpo as a neurotherapeutic agent, basic data *in vivo* must be obtained. Nothing is known about the pharmacology of very-high dose rEpo in this population."

(b) An October 29, 2001 response from the principal investigator to the ACH IRB regarding whether the above-referenced research constitutes a safety or safety/efficacy study states:

(i) "I would classify it as neither. Using the NICHD [National Institute of Child Health and Human Development] classification this is a phase I trial. Like many phase I trials it contains some preliminary elements but it was not powered to test efficacy."

(ii) "Note that this very high dose of rEpo (5000 U/kg as a single dose) has never been administered in a systemic fashion to human neonates. Thus, to proceed with this approach, a phase I study is needed first."

(c) A March 6, 2002 response from the principal investigator to the ACH IRB regarding the IRB's request that the investigator obtain an investigational new drug application (IND) from the Food and Drug Administration states:

"We obtain an IND when dealing with an approved product (taken verbatim from the web-site you quoted [www.fda.gov/cder/about/smallbiz/faq/htm]) 'when the principal intent ... is to develop information about the product's safety or efficacy ...' As you know, this phase I trial, and it's [*sic*] principal intent is biological effect, not safety (phase II) and not efficacy (phase III). Furthermore, item #3 (significantly increases the risks associated with the use of the drug

> product) does not apply since studies in adult humans and experimental animal give no indication whatever about added risk."

(d) Regarding OHRP's question relating to the lack of dose escalation in the above-referenced research, the May 23, 2003 report from USF and ACH states:

> "The premise of the study found solid support in previous research that showed that the high-dose (5,000 U/kg) maximized the potential for crossing the blood-brain barrier. Subjecting neonates to lower doses would, in the opinion of the IRB and the PI, expose the subjects to risks without any possibility of benefit.

OHRP further notes that the USF and ACH report later implies that the IRB approved the research under HHS regulations at 45 CFR 46.406, which suggests that the IRB believed that the above-referenced research did not hold out the prospect of direct benefit to the subjects. In addition, OHRP notes that the potential for blood-brain barrier penetration was described from previous work in a fetal sheep model, without any accompanying human data.

(e) USF and ACH's May 23, 2003 report indicated that the IRB reviewed and discussed the medical literature on dosing of erythropoietin, and in particular an article in the *Journal of Pediatrics* (J. Ped. 138(5):710-4, 2001), during its deliberations concerning the above-referenced research. OHRP notes that this article involves children, ages 5 - 20, undergoing long term hemodialysis. In addition, the article describes two groups of subjects (i.e, high-dose and average-dose) with mean erythropoietin doses of 714 ± 153 U/kg/wk and 295 ± 92 U/kg/wk, respectively.

OHRP finds that the ACH IRB lacked sufficient information to make the determinations required for approval of the above-referenced research under HHS regulations at 45 CFR 46.111. OHRP would expect that in order to make the necessary determinations at 45 CFR 46.111(a)(1) and (2), the IRB should have information regarding the administration of high-dose erythropoietin in the population under investigation. In the absence of such information, the IRB should have been provided a justification for the dose chosen, as well as a reason why a lower dose of erythropoietin was not utilized in this study.

Required Action: By October 7, 2005, please provide OHRP with a corrective action plan which adequately addresses the above determination.

(2) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. After reviewing the USF and ACH letters, OHRP notes that regarding the ACH IRB discussion of the IRB determinations under HHS regulations at 45 CFR 46.404-407, the USF and ACH letter dated May 29, 2003 states:

> (a) "The ACH IRB considered these regulations in their decision-making process. Although the use of these regulations and the determination of these specific findings were not fully documented in the minutes, they were the criteria that the ACH IRB used to determine if this research met the conditions of these regulations."
>
> (b) "While the minutes do not specifically reflect addressing the issues set forth in the [*sic*] 45 CFR 46.404-407, the minutes do reflect the appropriateness of this research in this population was [*sic*] an implied topic of discussion throughout the IRB deliberations."
>
> (c) "A review of the minutes, as referenced in *Question (2)*, provides an inference that the ACH IRB did consider the research to involve greater than minimal risk without the prospect of direct benefit. However, there is evidence in the minutes to support that the ACH IRB felt that this research would yield generalizable knowledge about the subject's disorder or condition (46.406)." [Emphasis in original]

Based upon the above statements and relevant IRB records, OHRP finds no evidence that the ACH IRB made the determinations required under HHS regulations at 45 CFR 46.404-407.

Corrective Action: OHRP acknowledges that the above-referenced research has been suspended. Furthermore, it is OHRP's understanding that the principal investigator is no longer employed at either institution. OHRP also acknowledges that the ACH IRB has modified its procedures to ensure that all future IRB discussions and determinations relating to 45 CFR 46.404-407 are documented in the IRB minutes. OHRP finds that these corrective actions adequately address the above determination and are appropriate under the USF and ACH FWAs.

In addition to the above determinations, OHRP notes that USF and ACH assert that the above-referenced research was approvable under 45 CFR 46.406. OHRP believes that due to the limited data available on the use of erythropoeitin in neonates, the unknown level of risk, and the nature of the proposed research, the above-referenced research likely did not satisfy the criteria for approval under HHS regulations at 45 CFR 46.404-406 and may have required review under HHS regulations at 45 CFR 46.407 if it were funded by HHS.

Please forward your corrective actions so that OHRP receives them no later than October 7, 2005.

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

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Barry Bercu, IRB Chair, USF
Dr. Paul Stiles, IRB Chair, USF
Ms. Norma Epley, Assistant Director, Research Compliance, USF
Ms. Holly L. Pageau, Administrative Research Coordinator, ACH
Dr. Atilano Lacson, IRB Chair, ACH
Dr. Lana Skirboll, NIH
Commissioner, FDA
Dr. David Lepay, FDA
Mr. Chris Pascal, ORI
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Shirley Hicks, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP