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April 18, 2013

Howard K. Koh, M.D., M.P.H.
Assistant Secretary for Health
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
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Rockville, MD 20852

RE: Neonatal Research Network Randomized Clinical Trials – Demand for OHRP Investigation and Suspension of Enrollment

Dear Assistant Secretary Koh and Dr. Menikoff:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to request emergency action by the Office for Human Research Protections (OHRP) — a program office within the Office of the Assistant Secretary for Health — to ensure that newborn premature and term infants are being adequately protected in seven current randomized trials being conducted by the Neonatal Research Network (NRN).

As you are aware, on April 10 we sent a letter to Secretary of Health and Human Services Kathleen Sebelius condemning the highly unethical Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) funded by the National Institutes of Health (NIH) and conducted by 23 academic medical institutions from the NRN.¹ Our letter highlighted egregious deficiencies in the SUPPORT study consent forms regarding the purpose, nature, and risks of the research that were uncovered by OHRP. Because the NRN researchers failed to disclose these critical pieces of information in the consent forms used in the SUPPORT study, there is reason for concern that the same inadequacies may exist in consent forms for the current, ongoing NRN clinical trials.

This situation is urgent: As each week goes by without assurances that parents of highly vulnerable subjects are being adequately informed about the nature and risks of these newer

¹ Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT Study. April 10, 2013. <http://www.citizen.org/documents/2111.pdf>. Accessed April 12, 2013.

experimental studies, more parents are potentially being deprived of information critical to making an informed decision regarding enrollment of their babies. As we pointed out in the case of the SUPPORT study, it is likely that many, if not most, parents would not have consented had they been fully informed about the purpose, nature, and risks of the research.

Our search of the ClinicalTrials.gov website reveals that the following randomized clinical trials funded by NIH and conducted by the NRN are either actively (six trials) or imminently (one trial) enrolling babies:

- (1) Evaluation of Systemic Hypothermia Initiated After 6 Hours of Age in Infants \geq 36 Weeks Gestation With Hypoxic-Ischemic Encephalopathy: A Bayesian Evaluation (primary endpoints: death or moderate or severe disability);²
- (2) A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for Extremely Low Birth Weight Infants With Necrotizing Enterocolitis or Isolated Intestinal Perforation (primary endpoints: death or neurodevelopmental impairment);³
- (3) Optimizing Cooling Strategies at $<$ 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy (primary endpoints: death or moderate-to-severe disability);⁴
- (4) A Randomized Controlled Trial of the Effect of Hydrocortisone on Survival Without Bronchopulmonary Dysplasia and on Neurodevelopmental Outcomes at 22-26 Months of Age in Intubated Infants $<$ 30 Weeks Gestation Age (primary endpoints: improvement in survival without physiologically defined moderate-to-severe bronchopulmonary dysplasia, and survival without moderate or severe neurodevelopmental impairment);⁵
- (5) Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in Extremely Low Birth Weight Infants (primary endpoint: neurodevelopmental outcome; death is one of the secondary endpoints);⁶
- (6) Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy? (primary endpoints: death or significant neurodevelopmental impairment);⁷ and
- (7) A Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Hypoxic-Ischemic Encephalopathy in Premature

² <http://clinicaltrials.gov/ct2/show/NCT00614744>. Accessed April 12, 2013.

³ <http://clinicaltrials.gov/ct2/show/NCT01029353>. Accessed April 12, 2013.

⁴ <http://clinicaltrials.gov/ct2/show/NCT01192776>. Accessed April 12, 2013.

⁵ <http://clinicaltrials.gov/ct2/show/NCT01353313>. Accessed April 12, 2013.

⁶ <http://clinicaltrials.gov/ct2/show/NCT01534481>. Accessed April 12, 2013.

⁷ <http://clinicaltrials.gov/ct2/show/NCT01702805>. Accessed April 12, 2013.

Infants 33-35 Weeks Gestational Age (primary endpoints: death or moderate or severe disability).⁸

A brief overview of these studies is enclosed. The total planned enrollment for these seven studies, six of which are currently enrolling infants, is more than 4,500 newborn infants.

Given the glaring deficiencies identified in the consent forms for the SUPPORT study discussed in our April 10 letter — forms apparently approved by the institutional review boards (IRBs) at 23 NRN medical centers participating in the study — there clearly is sufficient reason for the Department of Health and Human Services (HHS), OHRP, and the public to seriously doubt whether adequate and appropriate informed consent will be or was obtained from the parents of all newborn infants enrolling in these newer ongoing interventional trials also conducted by the NRN. Indeed, the public's confidence in the ethical integrity of human experimentation funded by HHS has been understandably shaken by the revelations about lack of informed consent in the SUPPORT study.

We therefore call on OHRP, using its authority to conduct compliance oversight investigations, to immediately obtain the IRB-approved protocols and consent forms from all institutions conducting all seven of these clinical trials, as well as any other ongoing NRN randomized trials not listed above. OHRP should ensure that each trial meets all requirements for IRB approval under HHS regulations for the protection of human subjects at 45 C.F.R. 46.111 and that the IRB-approved consent forms satisfy the informed consent requirements of HHS regulations at 45. C.F.R. 46.116.

Please note that in addition to concerns about the adequacy of consent in these studies, we also have serious concerns that the designs of some of the NRN studies listed above are unethical and violate the following provisions of the HHS human subjects protection regulations:

- (1) 45 C.F.R. 46.111(a)(1), which requires that, as a condition of approval, the IRB must determine that 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
- (2) 45 C.F.R. 46.111(a)(2), which requires that, as a condition of approval, the IRB must determine that risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

For example, the Transfusion of Prematures (TOP) Trial is comparing two different strategies for treating anemia (low red blood cell count/hemoglobin level) in extremely premature infants (birth weight of less than 2.2 pounds). The infants are randomly divided into two groups. Babies in one group receive blood transfusions whenever their red blood cell counts (hemoglobin levels) reach a moderately low target threshold (“liberal” transfusion group), and babies in the other group receive blood transfusions only when their red blood cell counts reach a severely low target threshold (“restricted” transfusion group). The researchers will then determine whether

⁸ <http://clinicaltrials.gov/ct2/show/NCT01793129>. Accessed April 12, 2013.

one group of babies has higher rates of death or long-term neurologic damage compared with the other group.

The TOP Trial as designed does not have a well-defined hypothesis. Through randomization in the study, subjects' clinical care with respect to anemia and blood transfusion management is being changed from the usual individualized care that is titrated based on the neonates' needs and a wide range of comorbid conditions, to experimental transfusion management based on different fixed levels of hemoglobin targets independent of perceived clinical need or an assessment of comorbid conditions. Because (a) the subjects are vulnerable premature infants struggling for life; (b) mortality is one of the primary outcomes of interest; and (c) the experimental study interventions for both groups have a risk of increasing patient mortality, minimization of risks to subjects necessitates inclusion of a control group that receives the usual routine transfusion management. The absence of an appropriate control group in the TOP trial precludes effective safety monitoring. For both experimental groups, increased rates of harm, including increased mortality, in comparison to patients receiving routine transfusion management may go undetected. As a result, the TOP Trial design fails to minimize risks to subjects.

Furthermore, such a study design almost certainly will result in harmful practice misalignments for a subset of subjects randomized to each group, a phenomenon well-described in the critical care and transfusion medicine literature.^{9,10,11,12,13,14} Such practice misalignments predictably may result in worse outcomes for the misaligned subjects in either experimental group in comparison to outcomes that would occur if the babies were managed according to usual, individualized blood transfusion management. Such treatment misalignments can seriously confound the results of a study, rendering the data uninterpretable. When this occurs, risks to subjects could *not* be reasonable in relationship to anticipated benefits, if any, to subjects, nor to the importance of the knowledge that may reasonably be expected to result.

Finally, OHRP should immediately order the suspension of new enrollment in the NRN studies listed above and in any other ongoing NRN randomized clinical trials not listed above until the agency completes its compliance oversight investigation. Enrollment in any particular trial should not be allowed to resume until OHRP confirms that the protocol, consent form content, and plan for obtaining consent are ethical and satisfy all HHS regulatory requirements.

⁹ Deans KJ, Minneci PC, Eichacker PQ, Natanson C. Defining the standard of care in randomized controlled trials of titrated therapies. *Curr Opin Crit Care*. 2004;10(6):579-82.

¹⁰ Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols. *Crit Care Med*. 2007;35(6):1509-1516.

¹¹ Minneci PC, Eichacker PQ, Danner RL, et al. The importance of usual care control groups for safety monitoring and validity during critical care research. *Intensive Care Med*. 2008;34(5):942-947.

¹² Deans KH, Minneci PC, Klein HG, Natanson C. The relevance of practice misalignments to trials in transfusion medicine. *Vox Sang*. 2010;99(1):16-23.

¹³ Deans KJ, Minneci PC, Danner RL, et al. Practice misalignments in randomized controlled trials: identification, impact, and potential solutions. *Anesth Analg*. 2010;111(2):444-450.

¹⁴ Deans KJ, Minneci P, Eichacker PQ, et al. Walk a mile in whose shoes? *Anesth Analg*. 2010;111(2):576-577.

In the wake of the disturbing revelations about the highly unethical SUPPORT study, agreeing to take these critically important actions would begin the surely lengthy process of restoring the public's confidence in the ethical integrity of HHS-funded research. Your refusal to take these urgently needed actions would only heighten the concerns millions of people in this country now have about the adequacy of HHS surveillance over human experimentation and, more important, would allow further recruitment of babies into potentially unethical, ongoing trials.

Please note that you may share this complaint letter with anyone. We will be posting it on our website and announcing it to major media outlets.

Thank you for your prompt attention to these important human subjects research issues. Please contact us if you have any questions.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

cc: The Honorable Kathleen Sebelius, Secretary of Health and Human Services
Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development, NIH
Dr. Kristina Borrer, Director, Division of Compliance Oversight, Office for Human Research Protections

Enclosure

Overview of Neonatal Research Network Randomized Clinical Trials Currently or Imminently Enrolling Newborn Infants

Evaluation of Systemic Hypothermia Initiated After 6 Hours of Age in Infants \geq 36 Weeks Gestation With Hypoxic-Ischemic Encephalopathy: A Bayesian Evaluation¹⁵

This study is assessing the safety and effectiveness of cooling the body (hypothermia) for 96 hours in infants (born at 36 weeks gestational age or older) who have evidence of hypoxic-ischemic encephalopathy (brain injury due to insufficient oxygen) at birth. The infants are randomly divided into two groups. Babies in one group have their body temperature lowered to 33.5°C for 96 hours starting between 6 and 24 hours after birth (hypothermia group). Babies in the other group have their body temperature maintained at a normal level (37°C). The researchers will determine whether one group of babies has higher rates of death or moderate-to-severe disability compared with the other group. The study began in April 2008 and is expected to continue until approximately March 2014. The researchers plan to enroll 168 infants.

A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for Extremely Low Birth Weight Infants With Necrotizing Enterocolitis (NEC) or Isolated Intestinal Perforation¹⁶

This study is comparing the effectiveness of two surgical procedures — laparotomy or drainage — commonly used to treat NEC or isolated small intestine perforation (a hole through the wall of the small intestine) in extremely premature infants (birth weight of less than 2.2 pounds). NEC, a common disorder in premature infants, causes necrosis (tissue death) in parts of the small intestine. It can progress to peritonitis (infection throughout the abdominal cavity) and shock. Babies with suspected NEC or isolated small intestine perforation who require surgical treatment are randomly divided into two groups. Babies in one group undergo laparotomy surgery, which involves making a relatively large incision in the wall of the abdomen, examining the intestines and abdominal cavity, and removing dead small-bowel tissue. Babies in the other group only have a drainage tube placed through a very small incision in the abdominal wall to drain fluid from the abdominal cavity. The researchers will determine whether one group of babies has higher rates of death or long-term neurologic damage compared with the other group. The study began in January 2010 and is expected to continue until approximately September 2015. The researchers plan to enroll 300 extremely premature infants.

Optimizing Cooling Strategies at $<$ 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy¹⁷

This study is assessing the safety and effectiveness of four different hypothermia treatment strategies based on target temperature and time in infants (born at 36 weeks gestational age or later) who have evidence of hypoxic-ischemic encephalopathy at birth. The infants are being randomly assigned to receive one of four cooling treatments:

¹⁵ <http://clinicaltrials.gov/ct2/show/NCT00614744>. Accessed April 12, 2013.

¹⁶ <http://clinicaltrials.gov/ct2/show/NCT01029353>. Accessed April 12, 2013.

¹⁷ <http://clinicaltrials.gov/ct2/show/NCT01192776>. Accessed April 12, 2013.

- Cooling to 33.5°C for 72 hours
- Cooling to 33.5°C for 120 hours
- Cooling to 32.0°C for 72 hours
- Cooling to 32.0°C for 120 hours

The researchers will determine the rates of death or moderate-to-severe disability for each group. The study began in September 2010 and is expected to continue until approximately March 2017. The researchers plan to enroll 726 infants.

A Randomized Controlled Trial of the Effect of Hydrocortisone on Survival Without Bronchopulmonary Dysplasia and on Neurodevelopmental Outcomes at 22-26 Months of Age in Intubated Infants < 30 Weeks Gestation Age¹⁸

This study is testing the safety and effectiveness of a 10-day course of treatment with the drug hydrocortisone for premature infants (estimated gestational age of less than 30 weeks) who are intubated (on a mechanical ventilator) at 14-28 days of life. The infants are randomly divided into two groups. Babies in one group receive hydrocortisone, and babies in the other group receive placebo. The researchers will determine whether infants in one group are more likely to survive without having moderate-to-severe bronchopulmonary dysplasia, a type of lung disease commonly seen in premature infants who need prolonged mechanical ventilation. They also will determine whether infants in one group are more likely to survive without having moderate-to-severe neurologic damage compared with the other group. The study began in September 2011 and is expected to continue until October 2016. The investigators plan to enroll 800 premature infants.

Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in Extremely Low Birth Weight Infants¹⁹

This study is comparing the safety and effectiveness of nonmaternal human milk versus preterm baby formula. The infants are randomly divided into two groups. Babies in one group receive pasteurized donated human breast milk, and babies in the other group receive formula milk developed for preterm babies. The researchers will determine whether babies in one group are more likely to die or have abnormal neurologic development compared with the other group. The study began in August 2012 and is expected to continue until June 2018. The researchers plan to enroll 670 premature infants.

Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy?²⁰

¹⁸ <http://clinicaltrials.gov/ct2/show/NCT01353313>. Accessed April 12, 2013.

¹⁹ <http://clinicaltrials.gov/ct2/show/NCT01534481>. Accessed April 12, 2013.

²⁰ <http://clinicaltrials.gov/ct2/show/NCT01702805>. Accessed April 12, 2013.

This study is comparing two different strategies for treating anemia (low red blood cell count or hemoglobin level) in extremely premature infants (birth weight of less than 2.2 pounds). The infants are randomly divided into two groups. Babies in one group receive blood transfusions whenever their red blood cell counts (hemoglobin levels) reach a moderately low target threshold (“liberal” transfusion group), and babies in the other group receive blood transfusions only when their red blood cell counts reach a severely low target threshold (“restricted” transfusion group). The researchers will then determine whether one group of babies has higher rates of death or long-term neurologic damage compared with the other group. The study began in December 2012 and is expected to continue until August 2017. The researchers plan to enroll more than 1,800 extremely premature babies.

A Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Hypoxic-Ischemic Encephalopathy in Premature Infants 33-35 Weeks Gestational Age²¹

This study will assess the safety and effectiveness of cooling the body for 72 hours in premature infants (born at 33-35 weeks gestational age) who have evidence of moderate-to-severe hypoxic-ischemic encephalopathy at birth. The infants will be randomly divided into two groups. Babies in one group will have their body temperature lowered to 33.5°C (hypothermia group). Babies in the other group will have their body temperature maintained at a normal level (37°C). The researchers will then see whether one group of babies has higher rates of death or moderate-to-severe disability compared with the other group. The study is expected to begin in May 2013 and continue until May 2018. The researchers plan to enroll 168 premature babies.

²¹ <http://clinicaltrials.gov/ct2/show/NCT01793129>. Accessed April 12, 2013.