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April 15, 2013

The Honorable Kathleen Sebelius
Secretary
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

RE: Neonatal Research Network Randomized Clinical Trials – Demand for Immediate Full Transparency and Suspension of Enrollment

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to request information and additional actions concerning seven current randomized trials on newborns, in follow-up to our April 10 letter 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 of the Neonatal Research Network (NRN).¹

A search of the ClinicalTrials.gov website reveals that the following randomized clinical trials funded by NIH and conducted by the NRN are either actively or imminently 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

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.

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.

- (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 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 is more than 4,500 newborn infants.

Given the egregious 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 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, as well as previous NRN trials that are no longer enrolling infants. 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.

In order to reassure the public — who is paying for this research — that the Department of Health and Human Services (HHS) is now actively taking appropriate steps to ensure the protections for these most vulnerable human beings, we demand that you immediately take the following actions:

- (1) Make publicly available on the HHS website all versions of the protocols, sample consent forms, and IRB-approved consent forms for (a) the seven clinical trials listed above; (b) any other ongoing NRN randomized clinical trials not listed above; and (c) all prior completed NRN clinical trials not listed above, so that they can be independently

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.

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

assessed by ethicists, researchers, and patient advocates unaffiliated with NIH and the NRN, as well as by any other interested member of the public. Most, if not all, of these documents must exist in digital form and could be easily posted to the HHS website immediately.

- (2) Order the suspension of new enrollment in the NRN studies listed above and in any other ongoing NRN randomized clinical trials not listed above. Enrollment in any particular trial should not be allowed to resume until you receive confirmation from independent experts that the protocol, consent form content, and plan for obtaining consent are adequate and appropriate.

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 actions would only heighten the concerns millions of people in this country now have about the adequacy of HHS surveillance over clinical trials.

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: Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development, NIH
Dr. Jerry Menikoff, Director, Office for Human Research Protections
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 Evaluation¹

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 Perforation²

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 Encephalopathy³

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

¹ <http://clinicaltrials.gov/ct2/show/NCT00614744>. Accessed April 12, 2013.

² <http://clinicaltrials.gov/ct2/show/NCT01029353>. Accessed April 12, 2013.

³ <http://clinicaltrials.gov/ct2/show/NCT01192776>. Accessed April 12, 2013.

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:

- 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 Age⁴

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 Infants⁵

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.

⁴ <http://clinicaltrials.gov/ct2/show/NCT01353313>. Accessed April 12, 2013.

⁵ <http://clinicaltrials.gov/ct2/show/NCT01534481>. Accessed April 12, 2013.

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?⁶

This study is comparing two different strategies for treating anemia (low red blood cell count) 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 are moderately low (“liberal” transfusion group), and babies in the other group will receive blood transfusions only when their red blood cell counts are severely low (“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 Age⁷

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.

⁶ <http://clinicaltrials.gov/ct2/show/NCT01702805>. Accessed April 12, 2013.

⁷ <http://clinicaltrials.gov/ct2/show/NCT01793129>. Accessed April 12, 2013.