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August 22, 2013

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

RE: 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?

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to express deep concern regarding the recurrence of serious ethical lapses in another clinical trial involving extremely premature infants — the Transfusion of Prematures (TOP) Trial — that is being funded by the National Institutes of Health (NIH) and conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD's) Neonatal Research Network (NRN). These ethical lapses, particularly with respect to the consent process, closely parallel those described in our April 10, 2013, letter¹ and subsequent May 8, 2013, letter and in-depth report² regarding another NRN study — the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). Unlike the SUPPORT study, in which concerns about serious ethical lapses were disclosed four years after subject enrollment was completed, the TOP trial investigators appear to be actively recruiting subjects at 15 different institutions (see Appendix). We therefore urge an immediate halt to the study due to the serious deficiencies in the consent forms and unresolved questions about the ethics of the study design.

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 August 21, 2013.

² Carome MA, Wolfe SM, Macklin R. Letter and report to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. May 8, 2013. <http://www.citizen.org/documents/2124.pdf>. Accessed August 21, 2013.

The TOP trial, interestingly subtitled “Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy,” is designed to primarily determine which of two strategies for treating anemia with blood transfusions is more likely to result in death or neurologic injury in extremely premature infants who develop anemia (low red blood cell or hemoglobin levels, hemoglobin being a component of red blood cells that carries oxygen from the lungs to the other organs in the body). The projected enrollment for the TOP trial is 1,824 infants. These highly vulnerable infants are to be randomly assigned to one of two groups, irrespective of their individual medical needs. In one group, the infants are to be transfused whenever their blood hemoglobin levels fall below a relatively high threshold level (liberal transfusion group). In the second group, infants are to be transfused when their hemoglobin levels fall below a very low hemoglobin level (restrictive transfusion group). Under the protocol, transfusions may be given to either group in exceptional urgent or emergent circumstances, even if the protocol-specified hemoglobin thresholds have not been reached. Of note, the best available evidence, previously published by some of the TOP trial investigators themselves and extensively cited in the TOP trial protocol, suggests, overall — as does the study’s subtitle — that the restrictive transfusion strategy is more likely to result in neurologic injury and other harms in extremely premature infants.

As in the SUPPORT study, the consent forms approved by the institutional review boards (IRBs) for the TOP trial — which, along with the complete TOP trial protocol, we obtained under a Freedom of Information Act request submitted to NIH — omit very important and material information regarding the purpose, nature, and risks of the experiment. Among the information not disclosed is the evidence from the aforementioned prior randomized trials suggesting that a restrictive transfusion threshold is more harmful than a liberal one. Furthermore, all of the consent forms include very misleading statements equating participation in the research with standard of care, and the majority of individual institutional consent forms indicate that the experimental interventions in the trial have no risk. As a result, the parents of potential TOP trial subjects are being denied the opportunity to make an informed decision about whether to enroll their infants in the research. It seems unlikely that any parent who fully understands the results of the prior clinical trials, as well as the true risks, purpose, and nature of the experiment, would be willing to enroll their premature infant in this study.

Additionally, and also as in the SUPPORT study, there are several unresolved serious ethical concerns regarding the design of the TOP trial and the adequacy of the IRB review of the research. In particular, we are very concerned about the lack of an appropriate control group that receives usual care (i.e., transfusions when needed based on individualized, patient-specific clinical factors) and the lack of a clear description of the pretrial standard transfusion practices at the NRN centers participating in the TOP trial. Given the former, adequate safety monitoring of the trial is not possible and as a result, risks to subjects are not minimized and reasonable in

relationship to any benefits of the research.³ Given the latter, the IRBs that reviewed and approved the protocol: (a) would not have had sufficient information to understand the degree to which the experimental interventions deviate from the usual care at the NRN centers and the risks thereby posed by these deviations; and (b) could not determine whether risks to subjects are minimized and reasonable in relationship to any benefits of the research.

We therefore urge you to:

- (1) Order an immediate halt to the TOP trial, if you have not already done so per our prior request for such action.
- (2) Direct the Office of Human Research Protections (OHRP) to immediately open a compliance oversight investigation into the trial.
- (3) Direct OHRP to develop a plan for contacting the parents of subjects already enrolled in the trial and providing them with a complete and accurate description of the risks, purpose, and nature of the research.
- (4) Initiate an independent investigation of the Department of Health and Human Services (HHS) system for review and oversight of HHS-funded human subjects research to understand how the system failed so miserably in both the SUPPORT study and the TOP trial. This investigation should include an assessment of all entities within NIH and other HHS agencies that played a role in the review, approval, and funding and oversight of the SUPPORT study and TOP trial. In addition, given the widespread failures across multiple IRBs that reviewed and approved the SUPPORT study and TOP trial, HHS should determine what systemwide actions are needed to prevent such failures from recurring.
- (5) Identify and suspend any similarly unethical research involving premature infants funded by NIH or any other HHS agency.

We provide below a more detailed review of our concerns.

³ 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;34:942-947.

I. Background

A. Prior randomized clinical trials testing liberal versus restrictive transfusion strategies in extremely premature infants

Anemia is very common in extremely premature infants due to many factors, including the need to draw multiple blood samples for various clinical tests and the relative impairment of the neonatal ability in producing new red blood cells.⁴ Significant anemia can lead to inadequate delivery of oxygen to body organs, causing cardiac stress, apnea, brain injury, and other complications, including death in the most severe cases. To prevent such complications, the majority of extremely premature infants receive one or more blood transfusions.⁵ Although transfusion of red blood cells is generally considered to be very safe, such treatment does carry possible risks, including:^{6,7}

- Delays in the maturation of the immature infant's bone marrow and the ability of the baby to produce its own red blood cells;
- Volume overload and congestive heart failure;
- Transmission of certain infections, such as Human Immunodeficiency virus (HIV) and Cytomegalovirus (CMV);
- Adverse effects on blood potassium, calcium, and glucose levels;
- Iron overload, which may increase the risk of chronic lung disease (bronchopulmonary dysplasia), retinopathy of prematurity (an eye disease in premature infants that can lead to blindness), or necrotizing enterocolitis; and
- Transfusion reactions.

Deciding when — at what level of anemia — to transfuse a premature infant involves: (a) balancing the risks of anemia and those of blood transfusions; and (b) considering numerous individual patient factors, including the following:^{8,9,10}

⁴ Widness, JA. Pathophysiology of anemia during the neonatal period, including anemia of prematurity. *NeoReviews*. 2008;9(11):e520 -e525.

⁵ Maier RF, Sonntag J, Walka MM et al. Changing practices of red blood cell transfusions in infants with birth weights less than 1000 g. *J Pediatr*. 2000;136(2):220-4.

⁶ Ohls, R. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.

⁷ Martin RJ, Fanaroff AA, Walsh MC. "The blood and hematopoietic system." *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant* 9th edition. Mosby 2011. P1303-1374. print

⁸ Ohls, Robin. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.

⁹ Guillen U, Cummings JJ, Bell EF, et al. International survey of transfusion practices for extremely premature infants. *Semin Perinatol*. 2012;36:244-247.

- Current level of anemia;
- Active bleeding or coagulopathy;
- The degree of supplementary oxygen required;
- Level of respiratory support (e.g., intubation, positive pressure ventilation, nasal cannula);
- Age of the baby;
- Reticulocyte count (count of new red blood cells);
- The need for medication to help the heart pump blood (inotropic support); and
- Major comorbidities, such as heart disease or sepsis.

Other factors sometimes taken into account that support transfusion include:^{11,12}

- Lactic acidosis;
- Increasing episodes of apnea (stopping breathing);
- Persistent tachycardia (abnormally fast heart rate);
- Persistent tachypnea (fast breathing); and
- Poor weight gain.

Thus, decisions about when to transfuse premature infants are routinely based on a variety of individual patient-specific factors.

Results of two earlier, relatively large randomized clinical trials comparing liberal and restrictive experimental blood transfusion strategies in extremely premature infants were published between 2005 and 2009 in articles co-authored by some of the TOP trial investigators and are extensively cited by the TOP trial investigators in their protocol to justify their new study.¹³ One was a single-center trial conducted at the University of Iowa involving 100 infants (the IOWA study^{14,15}), and the other was a multicenter study conducted at 10 institutions in Canada, the U.S.,

¹⁰ Fanaro S. Blood transfusion in infants: techniques and adverse events. *J Matern Fetal Neonatal Med.* 2011 Oct;24 Suppl 1:47-9.

¹¹ Ohls, R. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.

¹² Fanaro S. Blood transfusion in infants: techniques and adverse events. *J Matern Fetal Neonatal Med.* 2011 Oct;24 Suppl 1:47-9.

¹³ Kirplani H, Bell E, D'Angio C, et al. 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 a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. <http://www.citizen.org/documents/2150a.pdf>. Accessed August 20, 2013.

¹⁴ Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics.* 2005;115(6):1685-91.

¹⁵ Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr.* 2006 Sep;149(3):287-9.

and Australia known as the Premature Infants in Need of Transfusion Study (the PINT study^{16,17}) involving 451 infants. The results of both studies combined suggest worse outcomes for the infants who were in the restrictive transfusion groups.

The IOWA study, which included 51 infants in the liberal transfusion group and 49 in the restrictive transfusion group, had the following findings:^{18,19}

- Sixteen percent of infants in the restrictive transfusion group versus 2% in the liberal transfusion group died or had significant brain injury (defined as grade 4 intraventricular brain hemorrhage or periventricular leukomalacia, a condition seen in premature babies that involves death of brain tissue) ($p < 0.05$).
- Infants in the restrictive transfusion group had statistically significantly greater and more severe episodes of apnea (periods when the infant stopped breathing) than the liberal transfusion group.
- Children in the restrictive transfusion group received approximately *nine-fold* more urgent or emergent rescue transfusions (on average per child) for “congestive heart failure ... ascribed to anemia; acute hemorrhage and presumed hypovolemia; frequent severe apnea refractory to drug treatment ... or request by a surgeon or anesthesiologist for preoperative transfusion” than those in the liberal transfusion group (17 in the restrictive transfusion group versus 2 in the liberal transfusion group, with an average number of transfusions per subject of 0.35 versus 0.04, respectively).²⁰

In more recent unplanned follow-up neuroimaging²¹ and developmental evaluations²² of a subset of the IOWA study subjects, there was some indication that contrary to initial findings, the

¹⁶ Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr*. 2006 Sep;149(3):301-307.

¹⁷ Whyte RK, Kirpalani H, Asztalos EV, et al. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. *Pediatrics*. 2009 Jan;123(1):207-13.

¹⁸ Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics*. 2005;115(6):1685-91.

¹⁹ Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr*. 2006 Sep;149(3):287-9.

²⁰ Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics*. 2005;115(6):1685-91

²¹ Nopoulos PC, Conrad AL, Bell EF, Strauss RG, Widness JA, Magnotta VA, Zimmerman MB, Georgieff MK, Lindgren SD, Richman LC. Long-term outcome of brain structure in premature infants: effects of liberal vs restricted red blood cell transfusions. *Arch Pediatr Adolesc Med*. 2011 May;165(5):443-50.

²² McCoy TE, Conrad AL, Richman LC, Lindgren SD, Nopoulos PC, Bell EF. Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion. *Child Neuropsychol*. 2011;17(4):347-67.

restrictive transfusion group may have fared better with regard to long-term neurodevelopmental outcomes. However, as recognized in the TOP trial protocol and by others,²³ these follow-up studies are marred by substantial attrition (~44%), resulting in a high likelihood of bias, seriously compromising the validity and any generalizability of the follow-up studies. Of note, children who were enrolled in the follow-up studies had significantly greater mean hematocrits in infancy than those who were lost to follow-up (hematocrit 44 versus 37, $p < 0.001$), demonstrating that there could have been a selection bias in the follow-up studies. Thus, these two follow-up studies are at best uninformative and at worse misleading, and these results should be discounted when assessing the totality of available data from the randomized clinical trials.

The PINT study, which enrolled 223 infants in the restrictive transfusion group and 228 in the liberal transfusion group, demonstrated the following:

- More infants in the restrictive transfusion group experienced one or more of the following components of the composite primary endpoint before first discharge to home: death, severe eye disease (retinopathy of prematurity), lung disease (bronchopulmonary dysplasia), or brain injury, although results were not significant (74% in the restrictive group versus 70% in the liberal group, $p = 0.25$)²⁴
- In subjects followed for 18 to 21 months, death or neurodevelopmental impairment occurred in 45% of restrictive transfusion group subjects and 38% of liberal transfusion group subjects ($p = 0.09$). The differences between the two study groups in mortality and the rates of neurological impairment outcomes (any neurological impairment, cerebral palsy, cognitive delay, severe visual impairment, and severe hearing impairment) were each less favorable for the restrictive transfusion group, but none were statistically significant.²⁵
- Infants in the restrictive transfusion group received twice as many urgent or emergent rescue transfusions (on average per child) “in the event of shock, severe sepsis, coagulation defects, surgery, or for unanticipated emergencies” than those in the liberal transfusion group (173 in the restrictive transfusion group versus 87 in the liberal

²³ Venkatesh V, Khan R, Curley A, New H, Stanworth S. How we decide when a neonate needs a transfusion. *Br J Haematol*. 2013 Feb;160(4):421-33.

²⁴ Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr*. 2006 Sep;149(3):301-307.

²⁵ Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, Heddle N, LaCorte M, Robertson CM, Clarke MC, Vincer MJ, Doyle LW, Roberts RS; PINTOS Study Group. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. *Pediatrics*. 2009 Jan;123(1):207-13.

transfusion group, with an average number of transfusions per subject of 0.78 versus 0.38, respectively).²⁶

- In a post hoc analysis presented by TOP trial investigators, there was a significantly higher incidence of cognitive delay (defined as Mental Development Index <85) in the restrictive group (44.9% in the restrictive transfusion group versus 33 percent in the liberal transfusion group).²⁷

Of these two prior randomized clinical trials, the PINT study should be given the most weight because it is multicenter and has a much larger subject enrollment. Nevertheless, data from both trials overall suggests that extremely premature infants fared worse under restrictive transfusion guidelines than under liberal transfusion guidelines.

Indeed, in a 2006 editorial following publication of the results of the IOWA and PINT studies, Dr. Edward Bell, the TOP trial vice chair, wrote the following:²⁸

The question remains of how far we can push the anemic preterm infant before transfusing him. Efforts to eliminate transfusions should be revisited in light of the **minimal benefits of restrictive transfusion practice** shown in these two trials and the **potentially major benefits of liberal transfusion practice** shown in the Iowa Trial. Perhaps the drive to eliminate transfusions by tolerating moderate to severe iatrogenic anemia should be halted until more information is available. **The advantage of fewer transfusions is small compared with the potential benefit of more liberal transfusions in protecting the brain.** [emphasis added]

B. Overview of the TOP trial²⁹

The TOP trial is to be conducted by at least 19 NRN centers across the country. The infants to be enrolled are between 22 and 29 weeks gestational age, weigh less than 1 kilogram (2.2 pounds),

²⁶ Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr.* 2006 Sep;149(3):301-307.

²⁷ Kirplani H, Bell E, D'Angio C, et al. 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 a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. <http://www.citizen.org/documents/2150a.pdf>. Accessed August 20, 2013.

²⁸ Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr.* 2006 Sep;149(3):287-9. PubMed PMID: 16939732.

²⁹ Kirplani H, Bell E, D'Angio C, et al. 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 a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. <http://www.citizen.org/documents/2150a.pdf>. Accessed August 20, 2013.

and are in their first 48 hours of life. As of July 19, 2013, 15 of 19 institutions within the NRN consortium are currently recruiting premature infants into the TOP trial, according to the entry for this trial at clinicaltrials.gov.³⁰

Like the PINT and IOWA studies, infants enrolled in the TOP trial are to be randomly assigned to one of two transfusion groups, largely irrespective of their individual medical needs. The table below indicates the target hemoglobin levels at which infants are to be transfused and shows that babies in the restrictive transfusion group have to become much more anemic before they are transfused according to the protocol-specified criteria.

Hemoglobin Thresholds for Transfusion in the TOP Trial (All units in gm/dl)

TOP				
Postnatal Age	Restrictive		Liberal	
Days	Resp. Support	No Support	Resp. Support	No Support
1-7	11	10	13	12
8-14	10	8.5	12.5	11
>15	8.5	7	11	10

The specifically stated primary aim of the TOP trial is to examine whether the composite primary outcome of death or significant neurodevelopmental impairment (evidence of brain injury) at 22 to 26 months corrected age is less common among preterm infants who, by transfusion practice, are maintained at higher hemoglobin levels (i.e., managed according to a liberal transfusion threshold) than in infants with restrictive transfusion thresholds.

Neurodevelopmental impairment is defined by cognitive delay (Mental Developmental Index <85), cerebral palsy, severe vision impairment, or severe hearing impairment.

Key stated short-term secondary outcome measures in the TOP trial include, among others:

- Survival to discharge without severe morbidity, defined as any of the following: bronchopulmonary dysplasia retinopathy of prematurity, or serious brain abnormality (grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, or ventriculomegaly);
- Serious brain abnormality on cranial ultrasound examination;
- Number of transfusions and number of donor exposures by red blood cell donors or other blood products; and
- Episodes of necrotizing enterocolitis of Bell stage 2 or higher, and time to full-time feeds.

³⁰ Transfusion of prematures trial (TOP). <http://clinicaltrials.gov/ct2/show/NCT01702805>. Accessed August 21, 2013.

In discussing the basis for selecting the two sets of thresholds for the restrictive and liberal transfusion groups, the TOP trial investigators stated the following in their protocol:³¹

We base our proposed transfusion thresholds on:

- i. The range of hemoglobin thresholds used clinically to guide transfusion decisions in the participating NICUs of the NICHD Neonatal Research Network;
- ii. A poll of the range of hemoglobin thresholds that would be acceptable to each neonatologist in an NRN site within the context of an RCT.

The low threshold values reflect more common practice, so this is considered the “usual treatment” group. In this group, the transfusion thresholds are similar to those used for the restrictive group in both the PINT and Iowa studies. The highest threshold for the liberal transfusion group was the highest acceptable to neonatologists at the majority of NRN centers.

The TOP trial protocol provides no specific data regarding the survey of transfusion thresholds in the participating NRN NICUs, nor does it describe all of the specific clinical parameters that would alter the threshold for transfusion in individual patients under usual care at these institutions. In addition, the TOP trial investigators’ statement that the low threshold values reflect more common practice at the NRN NICUs is somewhat surprising in light of the results of an international survey study that was co-authored by the chair and vice chair of the TOP trial (Dr. Haresh Kirpalani and Dr. Bell, respectively) and cited in the TOP trial protocol.³² This international survey involved 1,018 neonatologists from 11 countries, 67 percent of whom were in the U.S. Most notably, the thresholds selected for the restrictive transfusion group in the TOP trial are at, or in some cases substantially lower than, the 25th percentile of the threshold used by the neonatologists who participated in the international survey.

The two experimental groups have the following two features that in combination cause the study interventions to deviate from the usual care for infants not enrolled in the research:

- (1) The choice of transfusion thresholds at the extremes of current practice; and

³¹ Kirplani H, Bell E, D’Angio C, et al. 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 a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. <http://www.citizen.org/documents/2150a.pdf>. Accessed August 20, 2013.

³² Guillen U, Cummings JJ, Bell EF, et al. International survey of transfusion practices for extremely premature infants. *Semin Perinatol.* 2012;36:244-247.

- (2) Transfusion algorithms based on only two (age and respiratory support) of the many clinical factors that would otherwise be taken into account to varying degrees in the usual care setting. (Other factors routinely used to decide whether to transfuse an individual infant that are not considered under the experimental interventions include, among other things, oxygen requirement, reticulocyte count, degree of respiratory support, and the presence of tachycardia or tachypnea.³³)

As a result, some infants randomly assigned to the *liberal* transfusion group will be transfused at higher hemoglobin levels than they otherwise would if not enrolled in the research. On the other hand, some infants randomly assigned to the *restrictive* transfusion group either: (a) will be transfused at lower hemoglobin levels than they otherwise would if not enrolled in the research; or (b) will *not* receive transfusions at hemoglobin levels above the restrictive hemoglobin threshold when they otherwise would if not enrolled in the research.

The TOP trial investigators acknowledge that harm can come as the result of randomization to restrictive or liberal transfusion practices when the decision to transfuse is typically based on guidelines informed by multiple individual patient factors. The authors attempt to mitigate this potential harm by allowing clinicians to bypass the assigned clinical transfusion algorithm when an infant's condition warrants acute urgent or emergent rescue transfusion. However, similar rescue transfusion strategies did not eliminate the less favorable outcomes seen in the IOWA and PINT studies for subjects in the restrictive transfusion groups.

II. Serious Deficiencies of the IRB-Approved TOP Trial Consent Forms

Through a Freedom of Information Act request submitted to NIH, we obtained the consent forms that were approved by IRBs at 17 institutions participating in the TOP trial (see Appendix). Based on a review of the protocol and these IRB-approved consent forms, we have determined that the TOP trial has the same types of serious flaws in informed consent as in the SUPPORT study with respect to the disclosure of the risks, purpose, and nature of the research.

A. Reasonably foreseeable risks

HHS human subjects protection regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent for research, investigators provide subjects or their legally authorized representatives (in the case of the TOP trial, the parents of the premature infants) with a description of any reasonably foreseeable risks.

³³ Ohls, Robin. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.

The TOP trial poses a number of reasonably foreseeable risks to subjects. The random assignment of the premature infants to one of two thresholds of hemoglobin levels that are at either the high end or low end of the “usual range” — independent of certain clinical factors that would normally be taken into account in making transfusion decisions as part of routine care of an individual infant — clearly has the potential to alter the care that the premature infants would otherwise receive as part of usual care if they are not enrolled in the trial.

For example, it is likely that some infants randomly assigned to the restrictive transfusion group will receive, overall, fewer transfusions than they would otherwise receive as part of usual care if they were not in the trial. As a result, particularly in light of the results of the IOWA and PINT studies, reasonably foreseeable risks of the research include possible increased risks of brain injury, impaired neurologic development, apnea, and even death. Infants in the restrictive group are also at increased risk of needing urgent or emergent rescue blood transfusions.

In contrast, it is likely that some infants randomly assigned to the liberal transfusion group, which is identified as the experimental group, will receive more transfusions, overall, than they would otherwise receive as part of usual care if they were not enrolled in the trial. Thus, reasonably foreseeable risks of the research include the potential increased risk of:^{34,35}

- Delays in the maturation of the immature infant’s bone marrow and the ability of the baby to produce its own red blood cells;
- Volume overload and congestive heart failure;
- Adverse effects on blood potassium, calcium, and glucose levels;
- Iron overload, which may increase the risk of chronic lung disease (bronchopulmonary dysplasia), retinopathy of prematurity (an eye disease in premature infants that can lead to blindness), or necrotizing enterocolitis;
- Transmission of certain infections, such HIV and CMV; and
- Transfusion reactions.

Moreover, the inclusion of death and neurologic injury as components of the composite primary endpoint for the study, combined with the investigators’ acknowledged uncertainty regarding the impact of each of the two experimental transfusion strategies on these outcomes, also warrants inclusion of these events as reasonably foreseeable risks. Indeed, the main purpose of the study is to see which group will have more deaths or neurologic injury.

³⁴ Fanaro S. Blood transfusion in infants: techniques and adverse events. *J Matern Fetal Neonatal Med.* 2011 Oct;24 Suppl 1:47-9.

³⁵ Martin RJ, Fanaroff AA, Walsh MC. “The blood and hematopoietic system.” *Fanaroff and Martin’s Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant* 9th edition. Mosby 2011. P1303-1374. print

However, all of the 17 IRB-approved consent forms, to varying degrees, fail to adequately disclose these reasonably foreseeable risks. Based on our analysis of the 17 consent forms, key observations regarding the discussion of the research risks include the following:

(1) Only one consent form indicates that there may be an increased risk of death or disability associated with the two research interventions.

(2) Fifteen consent forms conflate the potential risk of the research with the risks of routine medical care outside the research context by stating the following or something very similar:³⁶

The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy.

(3) Four consent forms include the following misleading statement or a very similar one:³⁷

This study does not carry any additional risk to your baby if you choose to take part.

(4) One consent form includes the following misinformation:³⁸

There are no known risks at this time to participation in this study.

(5) Twelve consent forms indicate that giving too much blood may delay blood production by the infants' own bone marrow and that not giving enough blood may result in the infants not having enough hemoglobin to carry oxygen around the body.³⁹ However, these consent forms proceed to declare that such problems will not occur in this trial because the study avoids these extremes by transfusing within the ranges of hemoglobin level routinely used by doctors.

(6) None of the consent forms describe the likely increased need for infants assigned to the restrictive transfusion group to receive more of urgent or emergent rescue transfusions for "clinical need," as was clearly shown in the PINT and IOWA studies.⁴⁰

³⁶ *Ibid.*

³⁷ IRB-approved consent forms for the TOP trial. <http://www.citizen.org/documents/2150b.pdf>. Accessed August 21, 2013.

³⁸ *Ibid.*

³⁹ *Ibid.*

⁴⁰ *Ibid.*

- (7) Only two consent forms come close to presenting an appropriate description of the risks by presenting a more extensive, albeit incomplete, description of the different risk profiles for each experimental group. The following is an excerpt from of these:⁴¹

Possible risks with transfusions done to keep your baby's hemoglobin at a higher level include:

If your baby is randomized to the high group it may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. Increased administration of fluids may delay closure of the PDA. An increased number of transfusions may result in a higher amount of iron in your baby's body. Too much iron may increase the risk of chronic lung disease (also called BPD), retinopathy of prematurity (an eye problem in premature infants) or necrotizing enterocolitis

Possible risks with transfusions done to keep your baby's hemoglobin at a lower level include:

If your baby is randomized to the low group, they will receive fewer transfusions. A baby with a low hemoglobin level could lead to the baby not having enough hemoglobin to carry oxygen around the body. The frequency of apnea of prematurity may be increased, and weight gain may be slower.

B. Purpose of the research

HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent for research, investigators provide subjects or their legally authorized representatives with an explanation of the purposes of the research.

Given the primary aim of the study, the TOP trial investigators should be informing parents of potential subjects that the main purpose of the research is to determine whether extremely premature infants are more or less likely to die, or more or less likely to develop neurologic impairment (brain damage), if they are managed with a liberal versus restrictive blood transfusion strategy.

While the title of the study (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?) — which appears on 15 of the IRB-

⁴¹ *Ibid.*

approved consent forms⁴² — reflects the primary study aim, most parents of prospective subjects are unlikely to derive an understanding of the primary purpose of this trial from the complex language used in the title. A review of specific explanations of the purpose of the research in 17 IRB-approved consent forms reveals that only two include reference to assessing mortality and only five mention an assessment of neurodevelopment or development.⁴³ Thus, the majority of IRB-approved consent forms fail to clearly explain the most important purposes of the research.

Finally, in discussing the purpose of the study, all of the IRB-approved consent forms included a statement similar to the following:⁴⁴

When the hemoglobin falls below a certain level, doctors will transfuse the baby. However, we know that some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. The reason for this is that we do not know which level of hemoglobin is better. This study aims to help us find out when we should best transfuse babies.

This statement incorrectly implies that nothing is known about what hemoglobin threshold to use when deciding when to transfuse premature infants. None of the consent forms discuss the results of the major randomized studies prior to the TOP trial (the PINT and IOWA studies) which, as discussed above, suggest overall that there are worse outcomes with a restrictive transfusion strategy than a liberal one. Nor do the consent forms explain that the TOP trial investigators, as implied in the title of the study, are trying to definitively prove whether a liberal strategy is indeed safer than a restrictive one.

C. Description of the research interventions

HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, investigators provide subjects or their legally authorized representatives with a description of the procedures to be followed and identification of any procedures that are experimental.

In numerous ways and to varying degrees, all of the IRB-approved consent forms for the TOP trial fail to adequately describe the research procedures, identify the procedures that are experimental, and distinguish those procedures from the usual care the infants would receive if not enrolled in the research. Both study groups receive experimental interventions that are intended to alter the timing of blood transfusion decisions in comparison to transfusion decisions that would be made if they were not enrolled in the research. Not only do most of the consent

⁴² *Ibid.*

⁴³ *Ibid.*

⁴⁴ *Ibid.*

forms fail to clearly identify these experimental procedures and how they differ from usual care, but they clearly misrepresent the nature of the study interventions by stating that the two thresholds for transfusing infants enrolled in the trial are within the range of normal or usual care given to infants not in the research. In particular, we note the following:

- (1) As previously discussed, as part of routine care outside the research context, the hemoglobin level at which a particular premature infant would be transfused is routinely based on consideration of many individual patient factors, only some of which are taken into consideration in the experimental algorithms for the liberal and restrictive transfusion groups. Note also that an experimental algorithm based in part on a poll of hemoglobin thresholds that would be acceptable to neonatologists *in the context of a randomized clinical trial* is not the same as what the hemoglobin thresholds for blood transfusion would be in usual care outside of a clinical trial. None of the consent forms clearly describe how the research interventions deviate from the usual individualization of transfusion care in extremely premature infants not enrolled in the study.⁴⁵
- (2) Only two of the 17 IRB-approved consent forms identified the restrictive group as being the usual approach for infants not enrolled in the research at that institution.⁴⁶ None of the other consent forms explained how the thresholds used for the two experimental groups compared to those used at the institution where the infant would be hospitalized if not enrolled in the research.
- (3) Seven consent forms included the following misleading statement or one very similar to it:⁴⁷

This study does not alter the routine care of your baby.

- (4) Sixteen consent forms included the following uninformative and misleading statement that blurred the distinction between the two research interventions being tested and the individualized transfusion decisions that would occur for infants not enrolled in the research:⁴⁸

Both of these [hemoglobin threshold] levels [for determining when to transfuse blood] are in the usual range used by doctors in the NICU.

⁴⁵ *Ibid.*

⁴⁶ *Ibid.*

⁴⁷ *Ibid.*

⁴⁸ *Ibid.*

Given the nature of the TOP trial protocol, these deficiencies in the consent forms approved by the IRBs at 17 major academic medical centers regarding the research risks, purpose, and experimental procedures are disturbing, but perhaps not surprising, given what we now know about what occurred in the SUPPORT study, involving many of the same institutions and investigators. Like the SUPPORT study, such egregious consent deficiencies deprive parents of the opportunity to make an informed decision about whether to enroll their infants in the research and thus represent a serious violation of research ethics. Finally, it seems unlikely that any parent who fully understands the results of the prior clinical trials, as well as the true risks, purpose, and nature of the experiment, would be willing to enroll their premature infant in this study.

III. Ethical Concerns Regarding the Design of the TOP Trial

In addition to the clear deficiencies regarding the informed-consent process for the SUPPORT study, we have significant ethical concerns about the design of the study. In particular, it appears that the study as designed failed to satisfy the requirements of 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 any anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

While there are many features of the protocol that raise ethical concerns, we describe two primary features below.

A. Lack of a control group

The TOP trial involves extremely premature infants who are critically ill, have a high baseline mortality rate, and require customized neonatal intensive care unit management. As discussed above, as part of routine care for such infants, decisions regarding the level of hemoglobin at which to transfuse blood would be individualized, based on multiple clinical factors.

The trial involves randomization to two experimental groups in which a fixed low or high hemoglobin threshold is used to determine when to transfuse blood, without taking into account some of the many factors that would be considered in such blood transfusion decisions. However, the trial lacks a control group receiving usual individualized care. Through randomization, the care of subjects will be changed from the usual care — individualized transfusion management provided to infants not enrolled in the study — to one of two experimental fixed target levels of transfusion thresholds, independent of perceived clinical need or an individualized assessment of risks and benefits. Without a control group involving individualized, usual care, adequate safety monitoring cannot be conducted by the data safety

and monitoring committee. Subjects in both experimental groups may experience an increased incidence of one or more adverse outcomes, including death, because of harmful misalignments. Yet these may go undetected without an appropriate usual care control group.⁴⁹

Therefore, without an appropriate usual care control group, risks to subjects are not minimized, nor are they reasonable in relation to the anticipated benefits to the subjects or the knowledge to be gained.

B. Insufficient information on usual care

We are also concerned that the IRBs that reviewed the TOP trial were not provided with sufficient information to make the findings required under 45 CFR 46.111(a)(1) and (2). In particular, the TOP trial protocol lacks a robust, detailed explanation of the usual care regarding transfusion decisions in extremely premature infants at each of the participating NRN medical centers.

As noted above, the protocol indicates that the transfusion algorithm for triggering a transfusion in each experimental group was based on the range of hemoglobin thresholds used clinically to guide transfusion decisions at the participating NRN NICUs. But the TOP trial protocol only reports that the low threshold values reflect more common practice but otherwise provides no details about the survey of transfusion practices at NRN NICUs that apparently was conducted prior to development of the protocol. It is unclear whether the statement that the “low threshold values reflect more common practice” means that: (a) between the high and low transfusion thresholds, the low transfusion threshold is more common, or (b) the low transfusion threshold is the most common across the NRN centers. Knowing whether (a) or (b) is true is critical to understanding the degree to which the experimental interventions deviate from the usual care at the NRN centers and the risks thereby posed by these deviations.

To fully assess the risks of the trial and to fully understand how the experimental interventions would alter transfusion management of the subjects in each study group in comparison to usual care, the IRBs would need much greater detail about the results of the survey of usual transfusion thresholds across the NRN NICUs. This should include individual data for each center and summary data for all centers that include the range, mean, median, and interquartile range. The IRBs would also need a detailed description of all the clinical factors that are taken into account when determining when to transfuse an individual infant. It is very concerning that such important detailed information is lacking from the protocol. Without this information, determinations regarding whether the TOP trial satisfies the requirements of HHS regulations at 45 CFR 46.111(a)(1) and (2) cannot be made.

⁴⁹ 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;34:942-947.

IV. Conclusions and Requested Actions

As in the SUPPORT study, the IRB-approved consent forms for the TOP trial omit very important and material information regarding the purpose, nature, and risks of the experiment. Furthermore, the consent forms include very misleading statements equating the participation in the research with standard of care, and the majority indicate that the experimental interventions in the trial have no risk. As a result, the parents of potential TOP trial subjects have been and are still being denied the opportunity to make an informed decision about whether to enroll their infants in the research.

There are also unresolved serious ethical concerns regarding the design of the TOP trial and whether the research satisfies the requirements of the HHS human subjects protection regulations at 45 C.F.R. 46.111(a)(1) and (2).

We therefore urge you to:

- (1) Order an immediate halt to the TOP trial, if you have not already done so per our prior request for such action.
- (2) Direct OHRP to open a compliance oversight investigation into the trial.
- (3) Direct OHRP to develop a plan for contacting the parents of subjects already enrolled in the trial and providing them with a complete and accurate description of the risks, purpose, and nature of the research.
- (4) Initiate an independent investigation of the HHS system for review and oversight of HHS-funded human subjects research to understand how the system failed so miserably in both the SUPPORT study and the TOP trial. This investigation should include an assessment of all entities within NIH and other HHS agencies that played a role in the review, approval, and funding of the SUPPORT study and TOP trial. In addition, given the widespread failures across multiple IRBs that reviewed and approved the SUPPORT study and TOP trial, HHS should determine what systemwide actions are needed to prevent such failures from recurring.
- (5) Identify and suspend any similarly unethical research involving premature infants funded by NIH or any other HHS agency.

Thank you for your urgent attention to these matters. Please contact us if you have any questions or require any additional information.

Sincerely,

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Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health
and Human Development
Dr. Howard K. Koh, Assistant Secretary for Health, HHS
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borrer, Director, Division of Compliance Oversight, OHRP

APPENDIX: Institutions Participating in the TOP Trial

Brown University, Women & Infants Hospital of Rhode Island*§
Case Western Reserve University, Rainbow Babies and Children's Hospital*§
Children's Mercy Hospital*§
Cincinnati Children's Medical Center*§
Duke University Health System*§
Emory University*§
Indiana University*§
Research Institute at Nationwide Children's Hospital*§
Stanford University§
University of Alabama at Birmingham
University of Buffalo§
University of California, Los Angeles*§
University of Iowa*§
University of North Carolina at Chapel Hill§
University of New Mexico*§
University of Pennsylvania, Children's Hospital of Philadelphia*§
University of Rochester*§
University of Texas Health Science Center, Houston
University of Texas Southwestern Medical Center at Dallas*
Wayne State University*§

*Institutions actively recruiting as of July 19, 2013

§Institutions with IRB- approved consent forms released by NIH in response to a Freedom of Information Act request