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April 10, 2013

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

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to express serious concern regarding the grossly inadequate corrective actions required by your department's Office for Human Research Protections (OHRP), as evidenced by the agency's March 7, 2013, compliance-oversight determination letter to the University of Alabama at Birmingham (UAB)¹ regarding the highly unethical, multicenter research study referenced above. The study involved the use of two different target ranges of oxygen levels (low, 85% to 89% saturation; and high, 91% to 95% saturation) to treat extremely premature infants, a most vulnerable group of human subjects.

This trial, funded by the National Institutes of Health (NIH) and ironically called the SUPPORT study, involved 23 major academic medical centers and exposed 1,316 extremely premature infants to increased risks of either death or retinal damage, depending on which oxygen group they were randomized to. Many, if not most, of the subjects' parents likely would have refused to let their newborn infants participate in the study had they been adequately informed of, and understood, the purpose and known risks of the research, as well as the differences in the experimental oxygen management for both SUPPORT study oxygen groups compared to usual individualized oxygen management for premature infants available at those same hospitals.

In its March 7 letter to the UAB, the Department of Health and Human Services' (HHS's) OHRP noted multiple serious deficiencies in the SUPPORT study consent form approved by the institutional review board (IRB, a committee charged with conducting an ethical review of human subjects research) at this trial center. The agency also noted similar serious deficiencies in consent forms approved by at least 22 other IRBs at major academic medical centers that reviewed this study. Referring to UAB's consent form, OHRP's letter reported the following key observations (bolded emphasis added):²

¹ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf. Accessed March 27, 2013.

² *Ibid.*

1. **The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper [oxygen] range group.**
2. **While the form says that being in the *lower* range group may result in the *benefit* of decreasing the chances of developing severe ROP [retinopathy — eye damage — of prematurity], in the “Possible Risks” section it does not say that being in the *upper* range group may result in the greater *risk* of developing ROP.**
3. **The only risk related to the part of the study involving the two ranges of oxygen levels described in the “Possible Risks” section is the risk of the pulse oximeter [to measure oxygen saturation levels] to the infant’s skin.”**

OHRP’s letter to UAB further stated (emphasis added):³

The SUPPORT study was designed as an interventional study. It specifically enrolled very premature infants and randomized them to one of two levels of oxygen. **For many of those infants, the level of oxygen they received was different from what they would have received had they not participated in the study. A major purpose for doing this was to increase the likelihood that there would be a measurable difference in the outcomes of the two groups. The primary outcome of interest for the researchers was whether the infants would develop severe eye disease or would die before being discharged from the hospital.**

The institutions participating in the study were otherwise using a target oxygen saturation within the range of 85% to 95% for routine clinical care purposes. For infants whose parents chose not to be in the study, the oxygen would have been appropriately adjusted within this entire range to meet the specific individual needs of the infant, rather than attempting to confine the infant’s oxygen saturation to either the 85-89% range or the 91-95% range to meet the needs of the research, depending on the randomized group assignment of each infant.

Consistent with what had been known for decades, the SUPPORT study results demonstrated a statistically significant greater number of cases of serious retinal damage in the high-oxygen group compared with the low-oxygen group (see table below).⁴ In addition, as suspected for many years, the study revealed a statistically significant higher death rate in the low-oxygen group compared with those in the high-oxygen group.

As the table below shows, the absolute difference in the risk of serious retinal damage was 9.3% higher in the high-oxygen group compared with the low-oxygen group, representing an approximately 50% higher relative risk of serious retinal damage. On the other hand, the absolute difference in the risk of death was 3.7% higher in the low-oxygen group compared with the high-oxygen group, representing a 27% higher relative risk of death. These differences, particularly with respect to serious retinal damage, should have come as no surprise to anyone — except perhaps the uninformed parents of the subjects who participated in the research.

³ *Ibid.*

⁴ SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.

Table: Key Major Outcomes from SUPPORT Study

Outcome	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% Confidence Interval)
Severe retinopathy of prematurity	41/475 (8.6%)	91/509 (17.9%)	0.52 (0.37-0.73)
Death before discharge	130/654 (19.9%)	107/662 (16.2%)	1.27 (1.01-1.60)

Despite the egregious informed-consent omissions for the SUPPORT study, which caused parents to enroll their premature infants in this experiment under the false pretense that it was much safer for their infants than was known to be the case, OHRP has failed to demand adequate and meaningful corrective actions by HHS, the medical centers that conducted this research, and the IRBs that reviewed and approved it. At a minimum, such actions should have included:

- (1) A requirement that HHS issue a formal apology to the parents of all 1,316 infants who participated in the SUPPORT study. This apology should come directly from you and the NIH Director, and it should be accompanied by a complete divulgence of the information previously not disclosed about the (a) the purpose of the research; (b) the experimental nature of the oxygen interventions that were administered to the parents' babies; and (c) the real, substantial risks to their babies, some of whom subsequently may have died unnecessarily or suffered impairment of vision as a result of their participation in the study.
- (2) A requirement that each participating institution and reviewing IRB take corrective action to address the serious deficiencies identified by OHRP in the IRB-approved consent forms.

We urge you to promptly issue this apology and direct OHRP to immediately require additional corrective actions. In addition, further independent investigation is needed to understand how the HHS system for review and oversight of human subjects research failed so miserably during the process of reviewing, approving, and funding the SUPPORT study.

Below is a more detailed discussion of our concerns and requested actions.

Overview of the SUPPORT study

The SUPPORT study was a randomized, multicenter clinical trial that, in part, compared two target ranges of oxygen saturation, low (85% to 89% saturation) and high (91% to 95% saturation) in 1,316 extremely premature infants born between 24 weeks, 0 days and 27 weeks, 6 days of gestation.⁵ The primary outcome measure was a composite of severe retinopathy of prematurity (ROP) — a condition that frequently results in severe retinal damage and blindness

⁵ *Ibid.*

— *death before discharge from the hospital*, or both.⁶ Subjects were enrolled in the study from 2005 to 2009.⁷

In commenting on the SUPPORT study protocol and consent form template, OHRP noted the following (emphasis added):⁸

In particular, a non-invasive device known as a pulse oximeter, commonly used in clinical care, would be applied to the infant's foot or hand. That device measures the blood oxygen saturation (SpO₂), which is the percentage of hemoglobin in the infant's bloodstream that has oxygen bound to it. The amount of oxygen provided to the infant would then be adjusted to try to keep the SpO₂ within one of two discrete ranges of oxygen levels, *i.e.*, a "low" range of 85% to 89%, or a "high" range of 91% to 95%. Infants were randomly assigned to the low or the high range.

The investigators noted that the institutions participating in the study were using a range of 85% to 95% for clinical care purposes. In contrast, the oxygen level of an infant enrolled in the study would be confined to either the lower or the upper portion of the range received by infants not participating in the study. **Altering the range of oxygen level an infant was supposed to receive was a crucial part of the study design. By creating two groups receiving two discrete ranges of oxygen levels, the study increased the likelihood that there would be significant differences in outcomes observed between the two groups, as compared to a [hypothetical] study comprised of a group of the lower or the higher range and a group receiving a level of oxygen anywhere along the range of 85% to 95%.**

With regard to those possible differences in outcome, the researchers were specifically looking at both whether the infant survived, and whether the infant developed a fairly significant level of ROP (what is called "threshold" disease). As the protocol put it, the primary hypothesis they were testing was "that relative to infants managed with a higher SpO₂ range that the use of a lower SpO₂ range will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention."

The protocol included the usual section entitled "Risks and Benefits." **That section did not identify any risks relating to randomizing subjects to the low or high range of oxygen...**

Given the complexity of these issues, it is worth summarizing some of the key points:

- a. The relationship between oxygen and development of severe retinopathy of prematurity had been examined for over 50 years. While the details of that relationship were not fully known, **it was well recognized that changing a**

⁶ *Ibid.*

⁷ *Ibid.*

⁸ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf. Accessed March 27, 2013.

premature infant's amount of exposure to oxygen could have an impact on a number of important health outcomes, including the development of severe eye disease (and possibly blindness); reduced neurologic development, including brain damage; chronic lung disease; and could even lead to death.

b. The SUPPORT study was designed as an interventional study. It specifically enrolled very premature infants and randomized them to one of two levels of oxygen. **For many of those infants, the level of oxygen they received was different from what they would have received had they not participated in the study. A major purpose for doing this was to increase the likelihood that there would be a measurable difference in the outcomes of the two groups. The primary outcome of interest for the researchers was whether the infants would develop severe eye disease or would die before being discharged from the hospital.**

c. **The template for the consent form used in this study did not mention any risks relating to the randomization between the higher and lower levels of oxygen, instead suggesting that this was a low risk study, noting that all of the treatments in the study were "standard of care," and that there was "no predictable increase in risk for your baby."**

d. While it would have been unwarranted to predict, ahead of time, specific outcomes (*i.e.*, which infants developed which outcomes), the researchers had sufficient available information to know, before conducting the study, that **participation might lead to differences in whether an infant survived, or developed blindness, in comparison to what might have happened to a child had that child not been enrolled in the study [and had gotten oxygen treatment suited to his or her individual clinical needs rather than the needs of the high or low oxygen groups in the study].**

Serious deficiencies of the IRB-approved SUPPORT study consent forms

In its March 7 letter to the UAB, OHRP stated the following regarding the IRB-approved consent forms for the SUPPORT study (emphasis added):⁹

We reviewed the UAB IRB records, including the study protocol, informed consent documents and data safety monitoring committee (DSMC) reports. **We also reviewed consent documents approved by 23 IRBs, and found problems with all of them similar to those described above with regard to the template consent form.**

The version of the UAB consent form provided to us (approved on June 4, 2008) provides the following information that is specific to the study of the levels of oxygen in premature infants:

⁹ *Ibid.*

At the front of the form:

“We will also be looking at the ranges of oxygen saturation that are currently being used with these same babies”.

In the section labeled “Introduction”:

“Another part of the study will be looking at the ranges of oxygen saturation that are currently being used with premature infants. Doctors, nurses, and others taking care of your baby use a machine called a pulse oximeter in routine daily care to help them adjust the oxygen to meet the baby’s needs. **Sometimes higher ranges are used and sometimes lower ranges are used. All of them are acceptable ranges.** In this part of the study, **we would like to pinpoint the exact range that should be used to help prevent some of the problems that occur with premature babies such as Retinopathy of Prematurity (ROP).** This is when there is abnormal blood vessel growth in the eye. It causes scar tissue to build up around the retina and if it pulls on the retina hard enough, it can cause blindness. It is known that ROP is increased by prolonged use of supplemental oxygen from observations published in the 1950s, but the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known. In going back and looking at how babies in the past were managed, it is being suggested that the use of lower saturation ranges may result in a lower incidence of severe ROP.”

In the section labeled “Procedures”:

“The babies in this study will also be placed randomly (again, like the flip of a coin) into a group monitored with lower oxygen saturation ranges or higher oxygen saturation ranges. Oxygen saturation is measured on a baby with a machine called a pulse oximeter. It uses a tiny sensor on the hand or foot of the baby and can give the doctors a measurement of how saturated the baby’s blood is with oxygen. Oximeters are not painful and can provide oxygen saturation measurements 24 hours a day. The babies in the lower range group will have a target saturation of 85-89%, while the babies in the higher range group will have a target saturation of 91-95%. **All of these saturations are considered normal ranges for premature infants.** If the saturation falls below 85% or goes higher than 95% then the pulse oximeter will alarm so that the doctors and nurses know when to turn your baby’s oxygen up or down.”

In the section labeled “Possible Benefits”:

“It is possible that using lower pulse oximeter ranges will result in fewer babies with severe Retinopathy of Prematurity (ROP).”

In the section labeled “Possible Risks”:

“There is no known risk to your baby from monitoring with the pulse oximeters used for this study. The possible risk of skin breakdown at the site will be

minimized by your baby’s nurse moving the oximeter to another arm or leg a couple of times a day.”

With regard to this information, OHRP notes the following:

- 1. The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group.**
- 2. While the form says that being in the *lower* range group may result in the *benefit* of decreasing the chances of developing severe ROP, in the “Possible Risks” section it does not say that being in the *upper* range group may result in the greater *risk* of developing ROP.**
- 3. The only risk related to the part of the study involving the two ranges of oxygen levels described in the “Possible Risks” section is the risk of the pulse oximeter to the infant’s skin.**

Based on the above facts, OHRP appropriately found that the IRB-approved consent form approved by the UAB IRB failed to adequately describe the risks of the research as required by HHS regulations at 45 C.F.R. 46.116(a)(2). In particular, OHRP noted the following (emphasis added):

According to the study design, on average, infants assigned to the upper range received more oxygen than average infants receiving standard care, and infants assigned to the lower range received less. Thus the anticipated risks and potential benefits of being in the study were not the same as the risks and potential benefits of receiving standard of care. For the infants assigned to the upper range, based upon the premises of the researchers, the risk of ROP was greater, while for the infants assigned to the lower range the risk of ROP was lower. And, as described above, there were also risks relating to neurological development and possibly death. The SUPPORT study involved changing the treatment of enrolled infants from the treatment of infants according to standard care, with attendant changes in the risks and potential benefits...

It would have been appropriate for the consent form to explain (i) **that the study involves substantial risks, and that there is significant evidence from past research indicating that the level of oxygen provided to an infant can have an important effect on many outcomes, including whether the infant becomes blind, develops serious brain injury, and even possibly whether the infant dies;** (ii) that by participating in this study, the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received, though it is not possible to predict what that change will be; (iii) that some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind; and (iv) **that the level of oxygen being provided to some infants, compared to the**

level they would have received had they not participated, could increase the risk of brain injury or death.

Although OHRP correctly determined that the IRB-approved consent forms for the SUPPORT study failed to disclose critically important information regarding the substantial, life-threatening risks of the research — and in fact misled parents of prospective subjects by essentially indicating that the research presented no risk — OHRP failed to identify other obvious, serious violations of the informed-consent requirements under HHS human subject protections regulations at 45 C.F.R. 46.116(a)(1). These regulations require that subjects or their legally authorized representatives (in this case, the parents of the premature infants) be provided, among other things, an explanation of the purpose of the research and identification of any procedures that are experimental.

- (1) With regard to the purpose of the research, the IRB-approved consent forms failed to disclose that one important purpose of the research was to determine whether the mortality rate of the infants would be different between the two experimental oxygen-management interventions.
- (2) With regard to identifying any experimental procedures, as explained clearly by OHRP, both subject groups received experimental interventions that altered the subjects' level of oxygen exposure in comparison to what they would have received as part of routine medical care, with one group receiving greater oxygen exposure and the other lower. Not only did the IRB-approved consent forms fail to identify these key experimental procedures, they instead clearly misrepresented the nature of the study interventions by stating that all subjects would receive oxygen treatments that maintained oxygen levels at "saturation . . . considered normal ranges for premature infants."

As part of routine care for such infants outside the research context, oxygen therapy would have been individually titrated with a goal of maintaining oxygen saturation levels somewhere within the range of 85% to 95%. Such individualized care would have been based on the parents' wishes for balancing the risks of administering lower levels of oxygen (including neurologic injury and death from hypoxemia [oxygen deprivation]) with the risks of administering higher levels of oxygen (including severe retinal injury, lung injury, and death from oxygen toxicity). Decisions regarding which oxygen level to administer to an individual premature infant routinely would be based on the outcome of ongoing discussions between the parents of the infant and the physicians caring for that infant. Some parents may choose a level of oxygen therapy for their infant that lowers the risk of neurologic injury and death from hypoxemia at the expense of increased risk of serious retinal damage. Other parents may choose an oxygen-management strategy that minimizes the risk of severe retinal damage at the expense of increased risk of neurologic injury and death from hypoxemia. Thus, determining which level of oxygen to administer as part of routine care is based on what is in the best interests of that infant, as determined by the infant's parents in conjunction with the infant's physicians and other members of the health care team.

Given the nature of the SUPPORT protocol as described by OHRP in its March 7 letter¹⁰ and by the investigators in published journal articles,^{11,12} these deficiencies in the IRB-approved consent forms regarding the research risks, purpose, and experimental procedures are extremely shocking. More disturbing is the fact that 23 IRBs at major academic medical centers all failed to recognize the deficiencies. Yet, it appears that UAB is the only institution required by OHRP to take corrective actions to address the consent-form deficiencies.

The failure to disclose such critically important information undoubtedly directly affected parents' decisions to enroll their premature infants in this study. It is highly likely that had they been appropriately informed about the nature of the research and its risks, many, if not most, parents would have declined to enroll their extremely premature infants in the SUPPORT study.

As a result of these deficiencies in the informed-consent process, the investigators of the SUPPORT study failed to obtain the legally effective informed consent from the subjects' parents, and the conduct of the study was highly unethical. Because this study was funded by NIH, the Department of Health and Human Services now has a moral obligation to formally apologize to the parents of all subjects enrolled in the study. This apology should come directly by you and the NIH Director, and it should be accompanied by a complete divulgence of the information previously not disclosed about (a) the purpose of the research; (b) the experimental nature of the oxygen interventions that were administered to the parents' babies; and (c) the real, substantial risks to their babies, some of whom subsequently may have died unnecessarily or suffered impairment of vision as a result of their participation in the study.

You also should direct OHRP to immediately take the following additional actions:

- (1) Expand its findings regarding the IRB-approved consent forms for the SUPPORT study to include the failure to accurately describe the purpose of the research and the failure to identify those research procedures that were experimental; and
- (2) Require substantive corrective action by each institution at which the IRB approved a seriously deficient consent form for the SUPPORT study. In addition to UAB, the institutions involved, according to the ClinicalTrials.gov registration¹³ for the trial and OHRP's March 7 letter, include:
 - Brown University
 - Case Western Reserve University
 - Duke University
 - Emory University School of Medicine

¹⁰ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf. Accessed March 27, 2013.

¹¹ SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959-1969.

¹² Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012;367(26):2495-2504.

¹³ ClinicalTrials.gov. Surfactant positive airway pressure and pulse oximetry trial (SUPPORT); ClinicalTrials.gov identifier: NCT00233324. <http://clinicaltrials.gov/ct2/show/NCT00233324>. Accessed March 28, 2013.

- Indiana University School of Medicine
- Sharp Mary Birch Hospital for Women and Newborns
- Stanford University School of Medicine
- Tufts Medical Center
- University of California, San Diego
- University of Cincinnati
- University of Iowa
- University of Miami Miller School of Medicine
- University of New Mexico Health Sciences Center
- University of Rochester School of Medicine and Dentistry
- University of Tennessee
- University of Texas Health Science Center, Houston
- University of Texas Southwestern Medical Center
- University of Utah School of Medicine
- Wake Forest University School of Medicine
- Wayne State University
- Women and Infants Hospital of Rhode Island
- Yale University School of Medicine

Unresolved ethical questions about the design of the IRB-approved SUPPORT study

In addition to the clear deficiencies regarding the informed-consent process for the SUPPORT study, there also are important unresolved ethical questions 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.

The SUPPORT study involved extremely premature infants whose clinical status was critically ill, requiring customized neonatal intensive care unit management. As discussed above, as part of routine care for such infants, oxygen therapy would have been individually titrated within an oxygen saturation range of 85% to 95%.

As OHRP noted, the study involved randomization to two experimental groups that involved attempting to confine oxygen saturation levels at either the high end or the low end of the range routinely used to manage such patients, but it did not include a control group. Through randomization, subjects were changed from what would have been individualized oxygen

management had they not participated in the study to different fixed target levels of oxygen management, independent of perceived clinical need or an individualized assessment of risks and benefits.

Based on research conducted long before the SUPPORT study and summarized by OHRP, it was highly plausible that targeting oxygen saturation at the high end of the usual range in premature infants would increase the risk of ROP, whereas targeting oxygen saturation at the low end of the usual range might increase the risk of neurological damage and death related to hypoxemia.

Given the available information, a strong argument can be made that any study comparing the two experimental target levels of oxygen saturation would be both unethical and not compliant with requirements of HHS regulations at 45 C.F.R. 46.11(a)(1) and (2).

We therefore urge you to direct OHRP to expand its compliance-oversight investigation of the SUPPORT study to include a careful re-assessment of the unresolved questions concerning the ethics of the study design.

Conclusions and summary of requested actions

In conclusion, the egregious deficiencies in the informed-consent process alone resulted in indefensible, highly unethical research involving vulnerable premature infants. While OHRP appropriately documented the serious informed-consent deficiencies related to the lack of disclosure of the risks of the research, the scope of OHRP's compliance-oversight findings for this research and the corrective actions being required by the agency are grossly inadequate.

In addition, the failure of at least 23 IRBs at major academic medical centers to recognize and correct the serious deficiencies in the sample consent form for the SUPPORT study is very troubling.

To ensure that the SUPPORT study deficiencies are meaningfully and adequately addressed and to prevent similar failures in the future, we again urge you to immediately take the following actions:

- (1) Issue a formal apology from you and the NIH Director to the parents of all 1,316 subjects enrolled in the SUPPPORT study. This apology should be accompanied by a complete divulgence of the previously undisclosed information regarding the nature, purpose, and risks of the research.
- (2) Direct OHRP to take the following actions:
 - (a) Expand the agency's findings regarding the IRB-approved consent forms for the SUPPORT study to include the failure to accurately describe the purpose of the research and the failure to identify those research procedures that were experimental;
 - (b) Require substantive corrective action by each institution at which the IRB approved the SUPPORT study;

- (c) Expand its compliance-oversight investigation of the SUPPORT study to include a careful re-assessment of the unresolved questions concerning the ethics of the design of the study.
- (3) 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 the case of the SUPPORT study. 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. In addition, given the widespread failures across multiple IRBs that reviewed and approved the SUPPORT study, HHS should determine what system-wide actions are needed to prevent such failures from recurring.
- (4) Identify and suspend any similarly unethical research involving premature infants that is funded by NIH or any other HHS agency.

Finally, this is another disturbing situation that may warrant the attention of the Secretary's Advisory Committee on Human Research Protections.

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

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
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borrer, Director, Division of Compliance Oversight, OHRP