Sept. 3, 2015

The New England Journal of Medicine Continues to Defend Unethical Clinical Trial Involving Premature Babies

Statement of Dr. Michael Carome, Director, Public Citizen's Health Research Group

Note: Late Wednesday, The New England Journal of Medicine (NEJM) published a perspective commentary online authored by Dr. John Lantos, a bioethicist at Children's Mercy Hospital in Kansas, Missouri, along with an editorial authored by the journal's editor in chief and other senior editors. Both pieces assert that a recent decision by the U.S. District Court for the Northern District of Alabama in Looney v. Moore *vindicate the investigators that conducted and the institutional review boards (IRBs) that approved the unethical Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).*

Public Citizen's Dr. Michael Carome previously worked at the U.S. Office for Human Research Protections (OHRP) as director of the Division of Compliance Oversight and associate director for regulatory affairs.

In April 2013, Public Citizen drew attention to an unethical clinical trial funded by the National Institutes of Health (NIH) that enrolled 1,316 premature infants, whose parents were not informed of the risks or the true nature and purpose of the research. The trial, known as SUPPORT, tested two experimental strategies for managing oxygen treatment in premature babies, with one group maintained at a low blood oxygen level and the other at a high level, as well as an experimental strategy for helping premature babies breathe.

The problems with SUPPORT were first identified by OHRP in the U.S. Department of Health and Human Services (HHS). In March 2013, OHRP wrote a letter to the University of Alabama at Birmingham (UAB), one of the lead institutions for SUPPORT, finding that the consent forms for the study did not disclose to the babies' parents any of the risks of the experimental oxygen management interventions, including risks of severe retinal damage, possible blindness, neurologic injury and death.

Public Citizen's subsequent analysis of the complete protocol and consent forms from more than 20 institutions not only affirmed the appropriateness of OHRP's determination, but demonstrated that problems with the consent form were far more significant than those discussed in OHRP's letter. In particular, the consent form failed to disclose the true purpose of the research and the nature of important experimental interventions. The trial's design also was ethically flawed.

Throughout the controversy surrounding SUPPORT, the editors of the NEJM, which published the primary results of the trial, have waged an ill-conceived campaign to defend the indefensible ethical failings of SUPPORT. The most recent volley in that defense came late yesterday when the NEJM published a perspective piece, *Vindication for SUPPORT*, by Dr. John Lantos and an accompanying editorial, *Support for SUPPORT*, by the NEJM senior editors.

In his article, Lantos reacts to the August 13 order granting summary judgment for the defendants in the lawsuit *Looney v. Moore* by Judge Karon Owen Bowdre in U.S. District Court for the Northern District of Alabama. The lawsuit, brought on behalf of three children who had been enrolled in the trial, was against UAB, the lead researcher for the trial, and the head of the IRB. The plaintiffs alleged that the babies suffered serious injuries as a result of participating in the trial.

Lantos's claims that the judge's ruling "appears to completely vindicate the investigators and the IRB" and that the "judge's analysis of the flaws in the reasoning of the plaintiffs' case has implications for an analysis of the OHRP's reasoning in its critique of the SUPPORT consent forms" seriously misrepresents the ruling. The judge's ruling was based on the holding that Alabama state law did not recognize a claim for increased risk of past harm, but only for actual harm incurred, and that the plaintiffs had failed to show that their specific injuries were "probably caused" by participation in SUPPORT. The judge, however, did not dispute that injuries to the three plaintiffs were possibly caused by participation in the study, including by the lack of informed consent.

Importantly, the judge's opinion offers no assessment, much less vindication, of the adequacy of the SUPPORT consent forms, trial design, and IRB review, or of OHRP's determination that the SUPPORT consent forms failed to disclose important reasonably foreseeable risks.

Relying on Lantos's arguments, the NEJM editors made the following preposterous statements:

> Once research is completed, it is unethical to retrospectively review consent forms in light of new knowledge that was gained by that research. OHRP owes an apology to the investigators and to the research community at large. Public Citizen, too, has fueled the controversy with campaigns of misinformation. Those campaigns have served only to make it harder to do the research we need to do to improve care. If the Public Citizen mindset were to prevail, we would still be treating heart failure with leeches and bloodletting.

First, Public Citizen's (and OHRP's) conclusions that SUPPORT consent forms failed to disclose the serious risks of the research did not depend on the results of the trial. The problems with the consent forms and the trial design should have been recognized by the reviewing IRBs *before* the study began.

Second, the claim that it is unethical to retrospectively assess the adequacy of informed consent based on new information that comes to light after a trial is completed is ludicrous. Unfortunately, too often in the history of human research, serious ethical violations have been identified well after studies were completed.

Third, OHRP is to be commended for standing up to powerful forces in the research community and consistently reaffirming its findings regarding the deficiencies in the SUPPORT consent forms. As we stated in 2013, it is the leadership of NIH and HHS who owe an apology to the parents of subjects who were misled about the nature and risks of the experimental procedures studied in SUPPORT.

Fourth, the NEJM editors' scurrilous charge that Public Citizen has engaged in a campaign of misinformation is without merit. Many experts in medicine, law, bioethics and other fields reached the same conclusions that we did regarding the deficiencies in the SUPPORT consent forms. Regrettably, the NEJM editors have published a series of misleading and unbalanced assessments of SUPPORT — pieces below the high standard of this prestigious journal.

Finally, Public Citizen strongly supports well-designed, ethical clinical research. Advocacy to ensure that human research is conducted in accordance with the highest ethical standards should not impede important advancements in medicine. To the contrary, we hope that it will prevent another travesty like SUPPORT from occurring.

To see OHRP's prior work regarding SUPPORT, click here.

###