SUPPORTing Premature Infants

AUTHOR: John D. Lantos, MD
Children’s Mercy Hospital, Kansas City, Missouri

KEY WORDS
ethics, oxygen toxicity, prematurity, research

ABBREVIATIONS
OHRP—Office for Human Research Protections
SUPPORT—Surfactant Positive Pressure, and Oxygenation Randomized Trial

FINANCIAL DISCLOSURE: Children’s Mercy Hospital is currently a member of the NICHD-funded Neonatal Research Network. It was not a member at the time of the SUPPORT study and Dr. Lantos was not employed there at the time of the SUPPORT study. At the time of SUPPORT, Dr. Lantos was employed at a hospital that was not a member of the NRN.

FUNDING: Supported, in part, by a Clinical and Translational Science Award grant from the National Center for Research Resources and the National Center for Advancing Translational Sciences awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research (UL1TR000001 [formerly UL1RR033179]). The contents are solely the responsibility of the author and do not necessarily represent the official views of the National Institutes of Health, the National Center for Research Resources, or the National Center for Advancing Translational Sciences. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page e1488, online at www.pediatrics.org/cgi/doi/10.1542/peds.2013-0878.

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) tried to determine the safest dose of oxygen for premature infants. The federal Office for Human Research Protections (OHRP) determined that the consent process for the study violated federal regulations by failing to inform parents of “reasonably foreseeable risks” of death or blindness.1 The New York Times agreed, calling these failures “startling and deplorable.”2 The New England Journal disagreed. They found the consent forms adequate and the accused the OHRP of “casting a pall over the conduct of clinical research.”3 Leaders of the NIH agreed.4 The difference of opinion turns, in part, on the ways that we define the relative risks of research, on the one hand, and, on the other hand, the risks of widely used but inadequately studied conventional therapies.

Ten years ago, Cole et al5 summarized the state of knowledge about oxygen therapy for premature infants: “We do not understand optimal oxygenation management in extremely low gestational age neonates (<28 weeks’ gestation). No randomized controlled trial has clarified the relation between retinopathy of prematurity and blood oxygen, transcutaneous oxygen, or oxygen saturation levels.” As a result, they noted, “neonatal care providers differ widely, with no consensus in their policies, practices, and strong beliefs regarding oxygen management in both the early and later neonatal courses of premature infants.” They called for prospective randomized trials to address this crucial gap in knowledge because “continued treatment of millions of premature infants in ignorance of what is safe and effective oxygenation is not an option.”

Today, the situation is different because such studies were designed and conducted in the United States,6 Canada, Australia, New Zealand, and the United Kingdom.7 In the United States, SUPPORT was a National Institutes of Health–sponsored, multicenter, prospective randomized trial of different strategies to treat lung disease in infants born at 24 to 27 weeks’ gestation. Between 2004 and 2009, ∼1300 infants were enrolled. The study led to a number of seminal articles that today, at long last, allow oxygen therapy to be evidence-based. Infants are safer as a result. However, questions are being raised about whether the studies harmed the infants who participated and about whether parents were fully informed about the risks of those studies.

On March 7, 2013, the federal OHRP notified the researchers in SUPPORT that “…the conduct of this study was in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage and death.”1 A month later, the consumer advocacy organization Public Citizen criticized the study even more harshly.8 They claimed that the study should never have been conducted because it had been “known for decades” that higher oxygen levels cause greater retinal damage. Furthermore, they claimed that the study entailed...
“real, substantial risks to...babies, some of whom subsequently may have died unnecessarily or suffered impairment of vision as a result of their participation in the study.” The New York Times weighed in with an editorial entitled “An Ethical Breakdown,” in which they called the study “startling and deplorable.”

However, the editors of the New England Journal of Medicine questioned OHRP’s reasoning and conclusions. They wrote that “there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants.” They concluded, “We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.”

In that same issue of the New England Journal of Medicine, the SUPPORT study researchers reviewed data which showed that the infants in the study were at no higher risk than infants who were not in the study. “The infants in both treatment groups had lower rates of death before discharge (16.2% in the higher-oxygen-saturation group and 19.9% in the lower-oxygen-saturation group) than did those who were not enrolled [emphasis added] (24.1%) and historical controls (23.1%), and rates of blindness did not differ between the treatment groups.”

So which is it? Was the study an egregious ethical breakdown? Or was it a model of how to make medical progress? To decide, one must look carefully at the critiques that OHRP made about the consent form. They found that the consent forms were deficient for not adequately conveying that: (1) the study involves substantial risks; (2) by participating in this study, the level of oxygen an infant receives would in many instances be changed from what he or she would have otherwise received, although it is not possible to predict what that change will be; (3) 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 (4) the level of oxygen being provided to some infants, compared with the level they would have received had they not participated, could increase the risk of brain injury or death.

Of these, only point number 2 is straightforward; the other points are arguable. Here’s why. The investigators did not believe that the study involved risk compared with the alternative of treating babies with oxygen doses determined by individual physicians based on the physicians’ clinical judgment. All available data show that infants in the study were safer — that is, they had lower rates of mortality — than comparable babies in similar NICUs at the same time. Similarly, it is not clear, as OHRP claims, that infants received more oxygen than they otherwise would have. Some perhaps did; others likely did not. Likewise, there is no evidence that even infants in the study, including infants in the higher oxygen group, had a greater risk of going blind than infants who were not in the study. Finally, there was no evidence that the level of oxygen provided to infants in the study increased the risk of brain injury or death compared with infants who were not in the study. The informed consent form accurately described the minimal risks. OHRP’s view was that it should have exaggerated the risks. This viewpoint does not seem like the correct standard for informed consent.

OHRP does not seem to understand that the clinical judgment of conscientious and knowledgeable physicians is only as good as the evidence on which it is based. They imagine that infants in the study would have been safer had their physicians made individualized clinical decisions.

Informed consent for research is a delicate process. It is especially delicate in pediatric studies that involve unstable and critically ill patients. These problems are illustrated in a study by Kapadia et al in this issue of Pediatrics. The authors randomized infants to receive different doses of oxygen during delivery room resuscitation. Such a study could only have been done with a waiver of the requirement for informed consent. To qualify for such a waiver, a study must be of only minimal risk. Kapadia et al argued that because both low and high doses of oxygen were consistent with 2005 NRP guidelines and because there was equipoise regarding the 2 treatment arms, the institutional review board permitted the trial to proceed without antenatal consent as long as parental informed consent was subsequently obtained from parents.” In other words, the institutional review board determined that the study was minimal risk. According to the criteria that the OHRP used to judge the SUPPORT study, however, the study by Kapadia et al would not be deemed minimal risk. Researchers and institutional review boards need to know the standards by which they will be measured. The controversy over the SUPPORT study is about what those standards should be. It illustrates just how much confusion exists today.

The research enterprise depends on safety, honesty, and transparency. The informed consent process is a crucial element in maintaining honesty and transparency. Consent forms should be as accurate as possible in describing the goals, methods, potential risks, and potential benefits of any research. But, in describing risks, we must be careful to accurately compare the risks...
of being in a study with the risks of not being in the study. When studies involve therapies that are in widespread use, and especially when there is documentation of widespread practice variation in the use of those therapies, infants who are in studies are not at higher risk by being randomized than are the infants who are not in studies and whose treatment depends not on the study design but on apparently random practice variation. In such situations, there may be no incremental risk to being in a study. There may even be some benefit.\textsuperscript{15,16}

We can and should always work to improve the process.\textsuperscript{17} Toward that goal, we should learn from the controversy about the SUPPORT study. But we should learn the right lessons. The most important lesson is that sometimes it is safer to be in a study than to not be in a study. An honest and transparent consent form should explain that concept. It is important information for potential study subjects to have as they decide whether they want to participate in a trial. A consent form might say something like this:

“We are studying two different doses of oxygen. We don’t know which dose is safer. If we knew, we wouldn’t be doing the study. Infants in one arm of the study may have better or worse outcomes than infants in the other arm. Or their outcomes might be the same. Infants in the study may have better or worse outcomes than infants who are not in the study. Again, if we knew that outcomes would be better in or out of the study, we wouldn’t be doing the study. We will carefully monitor outcomes for infants in the study and, as soon as it is clear that one treatment is better—or worse—than the other, we will stop the study.”

This description of the study honestly describes our uncertainty, that admission, in itself, might be stressful. Morris and Nelson\textsuperscript{18} noted that participation in randomized trials “confronts research participants and/or their families with the inadequacy of current medical knowledge, which may be upsetting.” The alternative, however, is to be dishonest about how little we know. Neither parents nor infants are served by a system that hides our uncertainty or one that is exquisitely attentive to the potential risks of randomized trials but oblivious to the greater risks of nonvalidated thera-

\begin{thebibliography}{18}


\bibitem{4} Hudson KL, Guttmacher AE, Collins FS. In support of SUPPORT – a view from the NIH. \textit{N Engl J Med}. 2013;368:2349–2351


\bibitem{8} Public Citizen. Letter to Secretary of Health and Human Services regarding ongoing clinical trials conducted by the Neonatal Research Network. Available at: www.citizen.org/2113. Accessed October 7, 2013


\bibitem{12} Lantos J. The weird divergence of ethics and regulation with regard to informed consent. \textit{Am J Bioethics}. 2013. In press

\bibitem{13} Luce JM, Cook DJ, Martin TR, et al; American Thoracic Society. The ethical conduct of clinical research involving critically ill patients in the United States and Canada: principles and recommendations. \textit{Am J Respir Crit Care Med}. 2004;170(12):1375–1384


\bibitem{15} Lantos JD. The “inclusion benefit” in clinical trials. \textit{J Pediatr}. 1989;134(2):130–131


\bibitem{17} Eder ML, Yamokoski AD, Wittmann PW, Kodish ED. Improving informed consent: suggestions from parents of children with leukemia. \textit{Pediatrics}. 2007;119(4). Available at: www.pediatrics.org/cgi/content/full/119/4/e849


\end{thebibliography}
SUPPORTing Premature Infants
John D. Lantos
Pediatrics 2013;132;e1661
DOI: 10.1542/peds.2013-1292 originally published online November 11, 2013;

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/132/6/e1661">http://pediatrics.aappublications.org/content/132/6/e1661</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 9 articles, 2 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/132/6/e1661.full#ref-list-1">http://pediatrics.aappublications.org/content/132/6/e1661.full#ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td><strong>Ethics/Bioethics</strong> <a href="http://classic.pediatrics.aappublications.org/cgi/collection/ethics:bioethics_sub">http://classic.pediatrics.aappublications.org/cgi/collection/ethics:bioethics_sub</a></td>
</tr>
<tr>
<td></td>
<td><strong>Fetus/Newborn Infant</strong> <a href="http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub">http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub</a></td>
</tr>
<tr>
<td></td>
<td><strong>Neonatology</strong> <a href="http://classic.pediatrics.aappublications.org/cgi/collection/neonatology:neonatology_sub">http://classic.pediatrics.aappublications.org/cgi/collection/neonatology:neonatology_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>
SUPPORTing Premature Infants
John D. Lantos
*Pediatrics* 2013;132:e1661
DOI: 10.1542/peds.2013-1292 originally published online November 11, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
[http://pediatrics.aappublications.org/content/132/6/e1661](http://pediatrics.aappublications.org/content/132/6/e1661)