SUPPORTing Premature Infants

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KEY WORDS

ethics, oxygen toxicity, prematurity, research

ABBREVIATIONS

OHRP—Office for Human Research Protections

SUPPORT—Surfactant Positive Pressure, and Oxygenation Randomized Trial

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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.”⁹

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.”¹⁰

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.*”¹¹

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.¹² 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.¹³ These problems are illustrated in a study by Kapadia et al¹⁴ 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.^{15,16}

We can and should always work to improve the process.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 Nelson¹⁸ 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 therapies.

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