The SUPPORT Controversy Continues

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INTRODUCTION

No doubt, the bioethics community recalls when in the spring of 2013, the Office for Human Research Protections (OHRP) sent a detailed letter to the principal investigator of the SUPPORT study admonishing the study team for its failure to provide adequate information about the study's risks in the consent forms.[1] Pandemonium ensued throughout the medical community as varying opinions formed regarding OHRP's assessment of the study. A few families of SUPPORT participants sued on the platform that their premature infants were harmed as a result of the study. Some years and hundreds of debates later, a federal judge threw out the suit this August, asserting that the families could not exclusively prove that the research study caused injury to participants.[2]

ANALYSIS

The SUPPORT study, which took place between 2004 and 2009, included at least 22 academic institutions nationally and was approved by approximately 23 institutional review boards. The study sought to determine the optimal oxygen saturation to provide premature infants in the Neonatal ICU (NICU).

In the past, Neonatologists have met difficulty in determining an effective level of oxygen saturation. Though it was originally thought that higher levels of oxygen would improve an infant's outcome, studies in the 1950's demonstrated increased cases of retinopathy of prematurity (ROP) (a condition often leading to blindness), with the administration of higher oxygen saturation. On the other hand, oxygen restriction can impair neurodevelopment or even result in death.

When the study began, the standard of care encompassed oxygen levels anywhere between 85-95%, with specific calibrations based on each child's individual circumstances. Thus the study, designed to determine how best to reduce ROP without producing other negative effects, addressed a crucial research question. The clinical trial assigned 1,300 infants born between 24-27 weeks to two different oxygen ranges— the low range (85-90%) and the high range (90-95%). It is important to note that the entire oxygen range remained within the standard of care, defining this as a comparative effectiveness trial. Published by the *New England Journal of Medicine* (NEJM) in 2010, the study revealed that babies in the low-oxygen group suffered statistically higher rates of death and those in the high-oxygen group developed significantly more cases of

ROP.[3]

Following the NEJM scientific publication, an OHRP official wrote the SUPPORT study's principal investigator, maintaining that the study violated "regulatory requirements of informed consent." OHRP, an agency that ensures the rights of participants in government-financed research, determined that the study failed to define the "reasonably foreseeable risks of blindness, neurological damage, and death."[1] The OHRP describes in its very detailed letter that the study did not thoroughly convey the risks in assigning patients to either arm.

The OHRP disclosed that while the "intended benefits" section boldly highlights a decreased chance of ROP for the lower level cohort, the consent's risk paragraph lacked the inclusion of any information about intended risks. The consent stated that since all treatments proposed were within the standard of care, no "predictable increase of risk for [a parent's] baby" existed.[1] In allocating participants to two extreme ranges within the standard of care, the researchers purposefully increased the probability of detectable differences between the groups. In the opinion of OHRP, infants assigned to the upper range would therefore receive, on average, a higher level of oxygen than standard care and the lower-oxygen cohort, the opposite.

Understandably, the OHRP's letter created quite an upheaval in the research community. A few weeks following the letter's public release, the editor in chief of NEJM, Dr. Jeffrey Drazen, and other NEJM affiliates authored an editorial condemning the OHRP's decision to "retrospectively" criticize the study in light of new knowledge gained from the published research.[4] Drazen et al affirmed that the increased risk of death proved a significant and unexpected finding of the study; if it had been known before the study began, standard clinical care would not have encompassed the lower oxygen range, and therefore, it would have been unethical to pursue the study. They claimed it was not a failure on the part of investigators to obtain informed consent from parents of participating infants. Drazen et al maintained this situation "casted a pall" over the conduct of clinical research, creating a greater barrier to the pursuit of answering important questions in daily practice.[4]

Others in the research community also stressed the distinction between risks associated with a study intervention, which must be disclosed in the informed consent document, and risks inherent to the illness being studied. Although the resultant trial focused specifically on harm done to the infants and not on the inadequacy of consent forms, the judge remarked, "correlation does not equal causation."[2] While the trial may have increased the babies' risk, the judge argued that their prematurity already placed them at very high susceptibility for injury.

Following the recent court ruling, Drazen et al published a second article in praise of the verdict, calling it a " victory for newborns, their parents, and all who spend their professional lives gathering the data we use in everyday practice of medicine."[5]

While some view this ruling as a positive for the research community, others point out that the trial did not address the key issue, that of informed consent. Bioethicists Ruth Macklin and Lois Shepherd found validity in the OHRP's original claims.[6] Macklin and Shepherd believe not one of the consent forms conveyed previous knowledge about the relationship between oxygen-level targets and mortality or that changing the oxygen ranges at which infants are maintained might affect whether an infant experiences a higher risk of death. Since the NICU already has a national registry of premature infants, a study with minimal additional risk could hypothetically be conducted through non-interventional collection of data. However, as Macklin and Shepherd maintain, the study clearly involved obvious risks, especially considering the low likelihood that infants outside the study would have been intentionally maintained in either the lower or higher oxygen targeted range. Furthermore, a similar study performed in the same time frame in New Zealand (BOOST), included the increased risk of ROP for the higher-level cohort and death/neurological damage for the lower range cohort. In my opinion, the fact that another country found it necessary to include these risks should further confirm that the U.S consent forms were inadequate.

CONCLUSION

As both a clinical research assistant at the NIH and a patient participant in trials myself, I can recognize all sides to this controversy. Research remains the keystone of medical progress, and we would be doing our world a disservice without performing trials like SUPPORT. On the other hand, transparency and ensuring patient safety remain essential components of research. I think Francis Collins and other NIH officials said it best when they released an editorial following the controversy, underlining the need for further discussion on how risks should be conveyed in the informed-consent process. Collins et al reminded us that the public debate surrounding the SUPPORT study has "set the stage" for a fundamental "national dialogue."[7]We must bring together research, advocacy and ethics communities in a quest to determine how best to not only respect and protect participants in research studies conducted within the standard of care, but also to define "reasonably foreseeable risks" in this setting.[7] Regardless of whether one agrees or disagrees with aspects of the debates surrounding SUPPORT, this situation has created an optimistic opportunity to better understand scientific and ethical issues that must be addressed when designing future studies.

[1] http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf

[2] U.S. District Court for the Northern District of Alabama Southern Division, Looney v. Moore. Case No.: 2:13-cv-00733-KOB (N.D. Ala. Aug. 13, 2015).

[3] 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;362:1959-1969

[4] Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. N Engl J Med 2013;368:1929-1931

[5] Drazen JM, Solomon CG, Greene MF, Support for SUPPORT. N Engl J Med September 2015. Online.

[6] Macklin R, Shepherd L, Dreger A, et al. The OHRP and SUPPORT — another view. N Engl J Med 2013;369:e3-e3

[7] Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D., N Engl J Med 2013; 368:2349-2351