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Notes


5. V. Sharav, HHS public meeting, August 2013, accessed February 8, 2014, https://www.youtube.com/watch?v=IAkBgyMxmtg&list=PLzt7E8KABz1Gc_nrd9gG8O_iEG51RNC&index=8.


Other Voices

SUPPORT: Risks, Harms, and Equipoise

by ROBERT M. NELSON

The debate about the ethics of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) often focuses on the assumptions made by the different parties involved, failing to note the lack of a necessary connection between those assumptions and the main criticism of the study—that the parents appear to have been poorly informed. The fact that the target ranges of oxygen saturation (SpO2) used in SUPPORT were within the range recommended as an appropriate “standard of care” does not mean that the infants randomized to one of two restricted SpO2 ranges received the same treatment they would have received outside of the trial. The corresponding observation that randomiza-


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tation altered the potential harms to which an individual infant was exposed does not mean that the risks of being in SUPPORT were greater than or in addition to the risks associated with usual care. The argument that parents should have been better informed about these potential harms does not entail the (incorrect) assumption that neonatal clinicians make individualized treatment decisions rather than follow a standardized protocol when adjusting the level of oxygen a preterm infant receives. The fact that parents are unaware of the trade-off clinicians make between these potential harms when establishing such a protocol does not justify the failure to adequately inform parents about the purpose of SUPPORT and the risks and harms that were involved.

John Lantos and Chris Feudtner are concerned that critiques about the inadequacy of the information provided to parents in SUPPORT involve flawed assumptions that, if generalized, could negatively affect comparative effectiveness research. They clarify that risk is the “group-level prevalence” (or probability) of experiencing a specific harm. The probability that an individual patient will experience that harm involves an inference based on the similarity of that individual to the group in which the risk was established. This clarification shows the importance of using the concepts of risk and harm carefully. Although we did not know, prior to SUPPORT, whether the “random shift in treatment would lead to benefit or harm for either group” of preterm infants—and thus could not ascertain the risk for any individual infant—the two groups of infants differed if they were randomly assigned to a treatment other than the one their clinicians would use outside of randomization. However, individual parents may have had a preference, as the potential harms to individual infants differed if they were randomly assigned to a treatment other than the one their clinicians would use outside of the study. Thus, death was not a “reasonably foreseeable” risk (although randomization altered the potential harms an infant was exposed to). Nevertheless, parents should have been informed about the potentials of death and NDI as part of the study purpose.

Henry Silverman and Didier Dreyfuss argue that the “additional foreseeable risks” of randomization to targeted SpO2 ranges were not justified by any anticipated clinical benefit. The protocol should have been modified to let clinicians adjust oxygen levels in response to changing clinical needs and to include a “usual-care” arm to allow for early termination based on safety needs. Their argument depends on a number of questionable assumptions about the superiority of usual care, however. In effect, they claim that SUPPORT as designed was not in sufficient equipoise. The argument that there was insufficient uncertainty within the neonatal community about the relative effectiveness of targeting the higher or lower SpO2 range is unfounded. After learning about the SUPPORT results and analyzing data from the original trials, the data and safety monitoring committees did not stop recruitment to the BOOST II trials. A subsequent interim analysis, after the pulse oximeter algorithm was modified to better separate the experimental arms, revealed an increased rate of death at thirty-six weeks for infants in the lower SpO2 range, and recruitment was terminated. This increased rate of death was not seen prior to modification of the SpO2 algorithm, suggesting that a usual-care arm would not have been informative and would not have allowed for early termination based on safety concerns. It would instead have been falsely reassuring. Early termination based on an increased incidence of ROP in the higher SpO2 group could have wrongly led to the conclusion that the lower SpO2 target range was safer. Further, in spite of the early termination of BOOST II and the SUPPORT results, the Canadian Oxygen Trial remained open following an interim data analysis, and the results of that trial did not confirm the findings of the other trials. In fact, the Canadian investigators caution against adopting the higher SpO2 limits given concerns about increasing the incidence of ROP. Thus, there appears to have been equipoise (that is, genuine uncertainty) in the neonatal community before and during the clinical trials.

SUPPORT is not an example of comparative effectiveness research between two generally accepted standards of care, given the oft-forgotten factorial protocol design. Prior to SUPPORT, there were no data suggesting that oxygen treatment based on clinician preference was better than using a protocol-based assignment strategy such as randomization. However, individual parents may have had a preference, as the potential harms to individual infants differed if they were randomly assigned to a treatment other than the one their clinicians would use outside of the study. Thus, the “reasonably foreseeable” risks and differential harms of protocol-driven treatments should have been disclosed, even if they were considered standard.
of care, to accommodate parents’ personal value judgments about the acceptability of different harms. The argument that we do not inform parents of these trade-offs as part of usual care merely highlights the inadequacy of clinical informed consent.\(^{12}\) In SUPPORT, parents should have been informed about the study’s purpose, the experimental procedures (including the altered pulse oximeter), the reasonably foreseeable risk of ROP in the higher SpO2 group, and the unforeseeable but potential harms of NDI and death in the lower SpO2 group.

**Disclaimer**

The opinions expressed in this commentary are solely those of the author and do not represent the policies of the Food and Drug Administration.


### Other Voices

**The Controversy over SUPPORT Continues and the Hyperbole Increases**

*by ALAN R. FLEISCHMAN*

Two articles in this issue of the *Hastings Center Report* address the continuing controversy over the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).\(^{1}\) This controversy is part of a larger discussion about the appropriate regulatory framework for protecting human research participants in comparative effectiveness research (CER), a group of studies that aims to compare two “usual” or “standard” treatments in order to provide evidence of which treatment is most effective.\(^{2}\)

Henry Silverman and Didier Dreyfuss argue that randomizing subjects to restrictive interventions at the outer limits of a standard-of-care practice, as was the case in SUPPORT, differs in important ways from treatment available outside of the proposed study and imposes additional reasonably foreseeable risks on the subjects. They conclude that the study not only required review by institutional review boards and an enhanced informed consent process revealing all of the reasonably foreseeable risks but also that local IRBs did not have the authority to approve the study because it contained significant risks that could not be justified by any compensating benefits to the subjects. They believe that the study required review and approval by the U. S. secretary of Health and Human Services. As they explain, federal regulations create four categories of permissible research involving children, and research in the fourth category, in which participants face significant risk without compensating benefit, requires the