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 authors and do not necessarily represent the official views of the National Institutes for Health or NCATS.

Notes

1. Office for Human Research Protection, letter to University of Alabama at Birmingham, October 12, 2014, http://www.mazzaschi.com/OHRP.6.4.2013.pdf.

2. G. J. Annas, "Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research," *Journal of Contemporary Health Law and Policy* 12 (1996): 297-324, at 297.

3. R. Faden et al., "Ethics and Informed Consent for Comparative Effectiveness Research with Prospective Electronic Clinical Data," *Medical Care* 51, no. 8, supplement 3 (2013): S53-S7.

4. M. A Carome, S. M. Wolfe, letter to Secretary of Health and Human Services in re The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), April 2013, accessed November 20, 2014, http://www.citizen.org/documents/2111.pdf.

5. V. Sharav, HHS public meeting, August 2013, accessed February 8, 2014, https://www.youtube.com/watch?v=IAfBKgYmxtg&list=PLrl7E8KABz1Gc_ndt9grGg8O_jE5G1RNC&index=8.

6. G. J. Annas and C. L. Annas, "Legally Blind: The Therapeutic Illusion in the SUPPORT Study of Extremely Premature Infants," *Journal of Contemporary Health Law and Policy* 30, no. 1 (2013): 1-36, at 4.

7. R. Macklin and L. Shepherd, "Informed Consent and Standard of Care: What Must Be Disclosed?," *American Journal of Bioethics* 13, no. 12 (2013): 8-14, at 10.

8. S. Hellman and D. S. Hellman, "Of Mice but Not Men—Problems of the Randomized Clinical Trial," *New England Journal of Medicine* 324 (1991): 1855-9.

9. F. G. Miller and D. L. Rosenstein, "The Therapeutic Orientation to Clinical Trials," *New England Journal of Medicine* 348 (2003): 1383-6, at 1384.

10. K. J. Barrington, "Personalized Medicine in the NICU," *American Journal of Bioethics* 13, no. 12 (2013): 33-35, at 34.

11. M. C. Morris and R. M. Nelson, "Randomized, Controlled Trials as Minimal Risk: An Ethical Analysis," *Critical Care Medicine* 35 (2007): 940-4, at 942.

12. E. J. Robinson et al., "Lay Public's Understanding of Equipoise and Randomisation in Randomised Controlled Trials," *Health Technology Assessment* 9, no. 8 (2005): 1-192.

13. L. M. Askie, D. J. Henderson, and H. Ko, "Restricted versus Liberal Oxygen Exposure for Preventing Morbidity and Mortality in Preterm or Low Birth Weight Infants," Cochrane Database of Systematic Reviews 4 (2001), art. no. CD001077, doi: 10.1002/14651858.CD001077.

14. K. Barrington, "Pre-SUPPORT, What Did We Really Know?," September 2013, accessed May 19, 2014, http://neonatalresearch.org/2013/09/07/pre-support-what-did-we-really-know.

15. J. E. Tyson, M. Walsh, and C. T. D'Angio, "Comparative Effectiveness Trials: Generic Misassumptions Underlying the SUPPORT Controversy," *Pediatrics* 134 (2014): 651-4.

16. J. D. Lantos, "The Weird Divergence of Ethics and Regulation with Regard to Informed Consent," *American Journal of Bioethics* 13, no. 12 (2013): 31-3.

17. J. F. Merz and D. Yarramilli, "SUPPORT Asked the Wrong Question," *American Journal of Bioethics* 13, no. 12 (2013): 25-26.

18. W. A. Carlo et al., "Target Ranges of Oxygen Saturation in Extremely Preterm Infants," *New England Journal of Medicine* 362, no. 21 (2010): 1959-69; B. J. Stenson et al., "Oxygen Saturation and Outcomes in Preterm Infants," *New England Journal of Medicine* 368, no. 22 (2013): 2094-104; B. Schmidt et al., "Effects of Targeting Higher vs Lower Arterial Oxygen Saturations on Death or Disability in Extremely Preterm Infants: A Randomized Clinical Trial," *Journal of the American Medical Association* 309, no. 20 (2013): 2111-20.

19. W. O. Tarnow-Mordi, B. Darlow, and L. Doyle, "Target Ranges of Oxygen Saturation in Extremely Preterm Infants," *New England Journal of Medicine* 363, no. 13 (2010): 1285.

20. Charles Natanson, testimony at HHS open meeting, August 2013, accessed October 23, 2014, http://www.hhs.gov/ohrp/newsroom/rfc/Public%20Meeting%20August%2028,%202013/supportmeetingtranscriptfinal.html.

21. A. Janvier, J. M. Lorenz, and J. D. Lantos, "Antenatal Counselling for Parents Facing an Extremely Preterm Birth: Limitations of the Medical Evidence," *Acta Paediatrica* 101, no. 8 (2012): 800-4; M. F. Haward, R. O. Murphy, and J. M. Lorenz, "Default Options and Neonatal Resuscitation Decisions," *Journal of Medical Ethics* 38, no. 12 (2012): 713-8.

22. E. Kodish et al., "Communication of Randomization in Childhood Leukemia Trials," *Journal of the American Medical Association* 291, no. 5 (2004): 470-75; R. N. Greenley et al., "Stability of Parental Understanding of Random Assignment in Childhood Leukemia Trials: An Empirical Examination of Informed Consent," *Journal of Clinical Oncology* 24, no. 6 (2006): 891-7.

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-

Robert M. Nelson, "SUPPORT: Risks, Harms, and Equipoise," *Hastings Center Report* 45, no. 1 (2015): 40-42. DOI: 10.1002/hast.415

tion 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.[1] 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 were exposed to different potential harms. Given this uncertainty about group probability, what risks ought to have been communicated to parents as being "reasonably foreseeable"?

The primary hypothesis of SUPPORT (regarding the use of supplemental oxygen) was to see if targeting a lower SpO2 range (85 to 89 percent) would increase survival without retinopathy of prematurity compared to when a higher SpO2 range (91 to 95 percent) was targeted.[2] Since oxygen induces ROP in premature infants, it could "reasonably" be expected that infants in the higher SpO2 group would have a higher probability of ROP. But it was not known whether a reduction in ROP would be offset by an increase in mortality or neurodevelopmental impairment.[3] Death as an outcome was included in the statistical analysis plan given the requirements of an intention-to-treat analysis (as a preterm infant may die before being evaluated for ROP or NDI). Death and NDI were also secondary outcomes, as the effect of targeting a lower SpO2 range on these outcomes was thought to be small.[4]

The neonatal community should be commended for designing five similar trials so that a metaanalysis on death and NDI could be performed, although questions have been raised about the timeliness of data sharing.[5] The data available before SUPPORT did not exclude an increased risk of death or NDI at the lower SpO2 range;[6] however, the expectation was that ROP incidence could be reduced without increasing mortality.[7] 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.[8] 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.[9] 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.[10] 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.[11] 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.

1. J. D. Lantos and C. Feudtner, "SUPPORT and the Ethics of Study Implementation: Lessons for Comparative Effectiveness Research from the Trial of Oxygen Therapy for Premature Babies," *Hastings Center Report* 45, no. 1 (2015): 30-40.

2. National Institute of Child Health and Human Development Neonatal Research Network, "The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial," August 28, 2004, last modified March 28, 2005, accessed November 29, 2014, http://www.nih.gov/icd/od/foia/library/Protocol.pdf; see, especially, p. 9.

3. C. H. Cole et al., "Resolving Our Uncertainty about Oxygen Therapy," *Pediatrics* 112, no. 6, part 1 (2003): 1415-19.

4. National Institute of Child Health and Human Development Neonatal Research Network, "The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants."

5. I. Chalmers et al., "Data Sharing among Data Monitoring Committees and Responsibilities to Patients and Science," *Trials* 14, no. 102 (2013), doi 10.1186/1745-6215-14-102; L. M. Askie et al., "NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration Study Protocol," *BMC Pediatrics* 11, no. 6 (2011): doi 10.1186/1471-2431-11-6.

6. L. M. Askie, D. J. Henderson-Smart, and H. Ko, "Restricted versus Liberal Oxygen Exposure for Preventing Morbidity and Mortality in Preterm or Low Birth Weight Infants," *Cochrane Database of Systematic Reviews* 1 (2009): CD001077.

7. Cole et al., "Resolving Our Uncertainty about Oxygen Therapy."

8. H. J. Silverman and D. Dreyfuss, "Were There 'Additional Foreseeable Risks' in the SUPPORT Study? Lessons Not Learned from the ARDSnet Clinical Trials," *Hastings Center Report* 45, no. 1 (2015): 21-29.

9. B. J. Stenson et al., "Oxygen Saturation and Outcomes in Preterm Infants," *New England Journal of Medicine* 368 (2013): 2094-2104.

10. B. Schmidt et al., "Effects of Targeting Higher vs Lower Arterial Oxygen Saturations on Death or Disability in Extremely Preterm Infants: A Randomized Clinical Trial," *Journal of the American Medical Association* 309 (2013): 2111-20.

11. M. S. Carome, S. Wolfe, and R. Macklin, "Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure That Risks Were Minimized," May 8, 2013, http://www.citizen.org/documents/2124.pdf; see p. 11 for a discussion of the factorial protocol design.

12. A. M. Capron, "The Real Problem Is Consent for Treatment, Not Consent for Research," *American Journal of Bioethics* 13, no. 12 (2013): p. 27-29.

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

Alan R. Fleischman, "The Controversy over SUPPORT Continues and Hyperbole Increases," *Hastings Center Report* 45, no. 1 (2015): 42-44. DOI: 10.1002/hast.416