EDITORIALS

Informed Consent and SUPPORT

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In the summer of 1963, the nation watched in sadness as Patrick Bouvier Kennedy, the youngest child of President John F. Kennedy and First Lady Jacqueline Bouvier Kennedy, was born prematurely and then died of lung disease 2 days later at Children's Hospital in Boston. Even now, it is common knowledge that children born prematurely are at high risk for death.

So it is easy to imagine the stress when, in 2005, your new baby decides to come into the world after only 6 months of gestation, long before your pregnancy has reached term. You know that extremely premature babies like yours may not survive, but you are reassured that you are giving birth at an academic medical center with a sophisticated nursery for premature newborns and with physicians who have extensive experience with very preterm infants. Decades of study and refining practice have resulted in major improvements in the care of premature infants; now most babies weighing a kilogram or more, and many weighing less than this, survive. This progress has come through careful research in multiple aspects of neonatal care, but many questions remain regarding practice that will maximize survival and minimize the long-term sequelae resulting from surviving severe prematurity. Without research studies, your neonatologist would simply be guessing about what is best rather than knowing what is best for your child.

The physicians in the nursery ask you to allow your very premature baby to participate in a research study, called the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), part of which is focused on the amount of supplemental oxygen they will give to your baby. They orally explain the study to you and ask you to sign an informed-consent document; it is six pages of single-spaced typescript.

Premature babies often require supplemental oxygen; what was not known in 2005 was exactly how much oxygen to give. The doctors knew that maintaining very high oxygen levels in the blood might cause retinopathy of prematurity (ROP), or abnormal growth of blood vessels in the eyes, which can damage the retinas and impair vision. The informed-consent form notes the higher risk of ROP that is associated with prolonged exposure to supplemental oxygen but states that "the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known" and also notes that "the use of lower saturation ranges may result in a lower incidence of severe ROP." Clinical practice at the time (and that recommended in the 2002 and 2007 guidelines of the American Academy of Pediatrics,[1,2] on whose guidelines committee one of us served) was to target values for the partial pressure of arterial oxygen anywhere between 50 and 80 mm Hg, consistent with oxygen saturations measured by pulse oximetry between 85% and 95%. Among the clinical questions addressed by SUPPORT was whether targeting the upper or lower end of this range might result in better outcomes for very preterm infants.

The study was conceived in 2003, initiated in 2005, and completed in 2009. Trials addressing the same clinical question were initiated in 2006 in the United Kingdom, Australia, and New Zealand (Benefits of Oxygen Saturation Targeting [BOOST II]), indicating the importance of the question.[3] For a baby not enrolled in any of these trials, the specific range of oxygen saturation targeted within these broader guidelines was left to the discretion of the

child's physician, who lacked data to guide decision making.

The consent document for SUPPORT that you have been handed spells this out clearly and succinctly: "The babies in the lower range group will have a target saturation of 85–89%, while the babies in the higher range group will have a target saturation of 91–95%. All of these saturations are considered normal ranges for premature infants." You sign the form, and your child enters the study. The same process was also taking place with parents of newborn extremely premature infants at multiple centers across the country.

After 5 years and more than 1300 babies studied, the data from SUPPORT are published in 2010 in the *Journal*.[4] The data show that, even within the recommended oxygen saturation range, babies with a higher oxygen saturation target had a higher risk of ROP, and those with a lower saturation target had a higher risk of death. With this new information, the investigators in the BOOST II trials in the United Kingdom and Australia review their preliminary data and discover that lower oxygen saturations in their trials are also associated with a higher rate of death.[3] These findings changed medical practice at many centers.

There was no way for you as a parent of a child in SUPPORT to know what the answer would be before your child participated. The study made clear that higher oxygen saturations within the then-recommended range increased the risk of retinopathy but decreased the risk of death. This is how new medical knowledge is gained. The story should have ended there, but it didn't.

In 2011, the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services began an investigation into the informed-consent process used when newborns were enrolled in SUPPORT. Their investigation concluded with a 13-page letter of determination sent to the SUPPORT lead center on March 7, 2013 (provided with a sample informed-consent form in the Supplementary Appendix, available with the full text of this article at NEJM.org). The OHRP reached the following conclusion: "It was alleged, and we determine, that the IRB [institutional review board] approved informed consent documents for this study failed to include or adequately address the following basic element required by HHS [Health and Human Services] regulations at 45 CFR 46.116(a): Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts."

This response is disappointing, because it does not take into account either the extent of clinical equipoise at the time the study was initiated and conducted or that the consent form, when viewed in its entirety, addressed the prevalent knowledge fairly and reasonably. At the time, as explained in the principal investigator's response to the allegations and in a related letter to the editor in the *Journal*,[5] 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. Through hindsight (and essentially faulting investigators for not informing parents up front of a risk later uncovered by the trial itself), the OHRP investigation has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice.

Clinical research is crucial if we are to advance medical science. Clinical investigators acted in good faith to design a trial to address an important question. An informed-consent document was drafted and approved by institutional review boards of participating centers before the work was begun. The OHRP has a duty to investigate questions of research impropriety, but we strongly disagree with their determination of inadequate informed consent in this case.

The results of SUPPORT have been critical in informing treatment decisions for extremely preterm infants. When babies like Patrick Bouvier Kennedy are born today, their chances of survival to adulthood are greatly improved, thanks to research made possible by thousands of parents and their children. We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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HCV Treatment — No More Room for Interferonologists?

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The landscape of therapy for hepatitis C virus (HCV) infection is changing rapidly. Until recently, the standard of care for HCV infection was a combination of peginterferon and ribavirin. Our increased understanding of the basic biology of HCV led to the identification of specific proteins involved in the replication of the virus. These proteins can be targeted by protease and polymerase inhibitors.

Two years ago, the advent of protease inhibitors, such as telaprevir and boceprevir, profoundly affected the field.[1,2] These agents improved the likelihood of cure but came with a number of inherent limitations. Protease inhibitors do not have antiviral activity in HCV genotypes other than the predominant genotype 1, which leaves at least five other HCV genotypes without coverage. Moreover, protease inhibitors can promote viral resistance, which usually signals therapeutic failure, and have multiple pharmacokinetic interactions with other drugs. Finally, protease inhibitors need to be administered with peginterferon and ribavirin, two drugs with extensive and well-established side-effect profiles that are aggravated by the addition of telaprevir or boceprevir.

Clinicians who treat patients with HCV infection have learned to accept and treat adverse effects as an integral part of patient care, but the inclusion of protease inhibitors in the therapeutic arsenal has added a layer of complexity. Indeed, the major challenge of contemporary interferon therapy is adequate management of side effects. Physicians and patients are ready for less toxic therapeutic options.

Two groups of investigators (Jacobson et al.[3] and Lawitz et al.[4]) now suggest in the *Journal* that change is about to happen. They describe the use of sofosbuvir, a novel polymerase inhibitor, in a series of four experimental studies targeting patients with HCV infection. In three randomized trials — FISSION, POSITRON, and FUSION — investigators focused on patients with HCV genotype 2 or 3, as seen in everyday clinical practice, including patients who had received no previous treatment, those who were unwilling to take interferon or had unacceptable side effects, and those who did not have a response to previous therapy. All the studies had a similar end point: a sustained virologic response at 12 weeks after the end of therapy. In addition, in the single-group, open-label NEUTRINO study, investigators studied the use of a sofosbuvir-based regimen in patients with genotype 1, 4, 5, or 6 infection.

The FISSION study examined the efficacy of 12 weeks of sofosbuvir plus ribavirin, as compared with the standard of care, peginterferon alfa-2a plus ribavirin, administered for 24 weeks. Standard therapy was successful in 78% of patients with genotype 2 infection and 63% of those with genotype 3 infection, as compared with rates of 97% and 56%, respectively, with the sofosbuvir-based regimen.

The POSITRON study evaluated a population that was not deemed to be eligible for interferon-based therapy and compared 12 weeks of sofosbuvir plus ribavirin with placebo. The primary reasons for ineligibility were a preexisting psychiatric disorder (57%) or autoimmune disorder (19%). None of the patients in the placebo group achieved the end point, but 93% of those with genotype 2 infection and 61% of those with genotype 3 infection had a sustained virologic response with sofosbuvir plus ribavirin.

The FUSION study, which targeted patients without a sustained response to interferon-based therapy, compared a 12-week regimen of sofosbuvir–ribavirin with a 16-week regimen. Four additional weeks of treatment made a difference, with an increase in the rate of sustained virologic response from 86% to 94% in patients with