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LEGALLY BLIND: THE THERAPEUTIC ILLUSION IN THE SUPPORT STUDY OF EXTREMELY PREMATURE INFANTS

George J. Annas* & Catherine L. Annas**

“Informed consent . . . is a moral requirement of both respect for autonomy and the good of the patient. It applies equally in the therapeutic and the experimental situation, and it is the responsibility of every physician.”

Edmund D. Pellegrino, MD

Physician-researchers follow a protocol to generate generalizable knowledge; physicians have a duty to treat patients in ways they and their patients think best. In both activities, research and treatment, physicians often see themselves simply as physicians, practicing medicine. Sick people have similar perception difficulties, and prefer to think of their physician-researcher simply as their physician, even when their treatment is determined by a protocol or the flip of a coin. 2 Almost 20 years ago, in this

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Journal, one of us suggested that at least some researchers use language “to obscure; to blur or eliminate the distinctions between research and therapy, scientist and physician, and subject and patient.” It was suggested that a major reason for the blurring was to “lower the standards for obtaining informed consent.” To prevent this, it was further suggested that it is necessary to firmly establish that the modern informed consent doctrine applies to both research and treatment. In this article we explore the recurrent problem of equating research and treatment, and its recurring (but misinformed) rationale—that in practice, informed consent only applies to research, and not treatment. Historically, misleading and confusing terms such as “therapeutic research,” “experimental treatment,” and “invalidated treatment” have been used to blur the distinction between research and treatment. Similar misleading terms are being deployed in an effort to make evidence-based medicine research (including comparative-effectiveness research) easier to do by dispensing with or watering down disclosure requirements. We agree with the great need to do more research on the safety and efficacy of currently used treatments, but strongly disagree that such research requires abandoning or diluting informed consent, or treating patients simply as passive objects for the valid purpose of improving the quality of care for all.

3. George J. Annas, Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research, 12 J. CONTEMP. HEALTH L. & POL’Y 297 (1996). The article argued, among other things, that seeing medical experiments as an integral part of searching for a “Holy Grail” (of any sort of medical care, such as curing cancer) suggests that the results will prove “miraculous,” but also that “blind devotion” to research and research protocols “produces uncritical action that can ultimately destroy values essential to human dignity.” Id. at 297.

4. Id. at 314-15. The substance of informed consent is the same in research and treatment, but what may be thought of as “procedural aspects” of informed consent vary. For example, federal research rules govern certain aspects of informed consent to research, including the requirement that it contain all the elements outlined in federal regulations, be set forth in a written consent form the research subject must sign, and the form itself has to be reviewed and approved by an Institutional Review Board before subjects can be recruited for a research project. Blurring the distinction between research and treatment, and following this blurring with a reduced or minimum consent requirement is the explicit goal of the “learning health care system ethics framework.” Ruth Faden, Nancy Kass, Steven Goodman, Peter Pronovost, Sean Tunis & Tom Beauchamp, An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics, 43 HASTINGS CENTER. REP. 1, S16 (2013). In the words of the proponents, their learning “framework rejects the moral relevance of the traditional distinction between research and practice . . . [and future work will develop criteria to determine] which activities require express prospective consent and which may be addressed by routine disclosures.” Id. at S24.
The latest term for conflating research and treatment is “standard of care research,” and the leading example that illustrates the problems with employing new and confusing terms for research is a study on extremely premature infants, the “Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial” (known as the SUPPORT study and described below). The (mistaken) belief that clinical practice on children does not require the informed consent of the parents explains, we think, why this seductive term, standard-of-care research, was invented. It seemed to justify, for example, not informing parents of the risks of death in each of the two possible groups to which their infant would be randomized in the SUPPORT study. Viewing research as treatment is a common mistake patients also make, so common that it has been given a name, the “therapeutic misconception,” or the “therapeutic illusion.”

We will suggest that in the SUPPORT study the SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Target Ranges of Oxygen Saturation in Extremely Preterm Infants, 362 NEW ENG. J. MED. 1959 (2010). The study had been planned in the early 2000s because, although the dangers of blindness as a result of giving too much oxygen to extremely premature infants was well known, the “lack of definitive evidence” on which to base treatment meant that “neonatal care providers differ[ed] 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.” Cynthia H. Cole, Kenneth W. Wright, William Tarnow-Mordi & Dale L. Phelps, Resolving our Uncertainty about Oxygen Therapy, 112 PEDIATRICS 1415, 1415 (2003) (proposing that “an adequately powered, large, randomized, controlled trial” be conducted). The study was proposed “to resolve the uncertainty and determine the impact of different ranges of oxygen levels or saturations, initiated early in the neonatal course, on ROP [retinopathy of prematurity] and other important outcomes such as mortality . . . .” Id. The study was to be designed to answer the question of whether using levels in the “lower” versus the “higher” range of oxygen saturation could “reduce the incidence of severe ROP without increasing important adverse neonatal outcomes.” Id. at 1416. The outcomes to be measured “include[d] severe ROP, blindness, bronchopulmonary dysplasia, growth, death, and different types of major neurodevelopmental or neurosensory impairment beyond infancy.” Id. at 1417. The authors noted that obtaining equipoise among neonatal units would be difficult when comparing 85-89% vs. 91-95% because “some neonatal units regard [greater than] 90% as mandatory” even though there is data that suggests oxygen can be reduced without increasing “mortality or cerebral palsy.” Id.

6. Annas, supra note 3; see also Jonathan Kimmelman, The Therapeutic Misconception at 25: Treatment, Research and Confusion, 37 HASTINGS CENTER REP. 6, 36 (2007). It should be noted that the acronym of the study, “SUPPORT,” lends itself to the therapeutic misconception, as it suggests therapy (“support”), rather than research. See infra notes 70-73 and accompanying text. This problem is also illustrated by the history of phase 1 cancer trials in the U.S. Sam Horng, Ezekiel Emanuel, Benjamin Wilfond, Jonathan Rackoff, Karen Martz & Christine Grady, Descriptions of Benefits and Risks in Consent Forms for Phase 1 Oncology Trials, 347 NEW ENG. J. MED. 26, 2134,
therapeutic illusion was strongest on the part of the researchers, sponsors, Institutional Review Boards (“IRBs”), and institutions, rather than, as is usual, on the part of the patient-subjects.

I. THE SUPPORT STUDY

The SUPPORT study, conducted by the 23 research hospitals that are part of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, was based on a 2 by 2 intervention design. Extremely premature infants (24 weeks, 0 days to 27 weeks, 6 days gestation) were randomized prior to birth to receive either early continuous positive airway pressure (“CPAP”) or early surfactant. The infants in both of these groups were then randomized again to receive oxygen saturation targeted at either 85-89% (low range) or 91-95% (high range). Since 1950 it was known that higher ranges of oxygen increased the risk of blindness. The hypothesis for the oxygen saturation component of the trial (the one we concentrate on in this article) was that:

[A] lower target range of oxygen saturation (85 to 89%), as compared with a higher range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity [which causes blindness] or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days gestation.

The hospitals participating in the SUPPORT study enrolled more than 1,300 infants from 2004 to 2009. Two aspects of the study became particularly controversial, both centered on informed consent: the extent to which the parents were adequately informed of the risks to their infants by participating in the study, and the extent to which the parents were properly informed of how the study would be conducted, especially that the instruments used to measure the oxygen saturation levels in their babies would be modified so that the readings they gave were inaccurate ones. Using the modified pulse oximeters meant that the team caring for their infant would not know the actual oxygen level their infant was getting. Specifically, under the protocol, in order to blind the researchers as to which oxygen arm the infant was in, the pulse oximeters, which measure the oxygen saturation levels in the blood, were altered to give inaccurate readings: in one group, the instrument showed saturation levels of 88 to 92%, even though the actual level was in the 85 to 89% range; and in the

2134 (2002). One study of 260 consent forms for phase 1 cancer trails, for example, termed the “investigational agent as ‘treatment’ or ‘therapy,’ without including modifying words such as ‘experimental’ or ‘research’” 96 percent of the time. Id. at 2136.

7. SUPPORT, supra note 5, at 1960.
other group the instrument showed saturation levels again at 88 to 92%, even though the true level in this group was in the 91 to 95% range. The maximum variation was 3%, so that in one arm of the study the true reading was 87% when the oximeter read 90%, and in the other arm of the study the true reading was 93% when the oximeter read 90%. Alarms were set to go off at the extremes (i.e. at the 85% level and the 95% level) to keep all actual levels within the 85-95% range, which was thought to be the range of accepted care (or standard care) for extremely premature infants in neonatal intensive care units (“NICUs”) around the U.S.

On March 7, 2013, the U.S. Office for Human Research Protection (“OHRP”), the federal agency within the Department of Health and Human Services (“HHS”) charged with overseeing institutions that conduct research, including federally-funded research, sent a 12-page letter to the University of Alabama at Birmingham (“UAB”) regarding SUPPORT. The letter summarized the investigation into a complaint that the research was not done in compliance with OHRP’s regulations, specifically that the consent form did not properly disclose the risks of participating in the study. The consent form listed the following:

**Possible Benefits:**

It is possible that using lower pulse oximeter ranges will result in fewer babies with severe Retinopathy of Prematurity (ROP).

**Possible Risks:**

8. *Id.* at 1960. It is worth underlining early that, although this research was often characterized as “standard of care” research (comparing two oxygen ranges that were within the ranges physicians were using before the study was done), in fact no physician in practice was blinding themselves to what the actual oxygen levels were for their tiny patients by using a measuring device that was calibrated to give inaccurate readings, and few, if any, physicians were maintaining oxygen levels at either extreme of the range, but rather were raising or lowering oxygen levels depending on how their patients were doing based on physical assessments and other clinical measurements. *See also* Tuyet-Hang Nghiem, James I. Hagadorn, Norma Terrin, Sally Syke, Brenda MacKinnon and Cynthia H. Cole, *Nurse Opinions and Pulse Oximeter Saturation Target Limits for Preterm Infants*, 121 PEDIATRICS e1039 (2008). A 2004 survey of neonatal ICUs found “acceptable” ranges from 80% to 100%, where “the range of lower limits was 80% to 92% . . . and the range of upper limits was 92% to 100%.” *Id.* at e1041. It should also be noted that, while almost all of the commentary on SUPPORT has involved the ethics of consent, the design of the trial itself has also been questioned—although this issue is beyond the scope of this article. *See, e.g.*, infra notes 54 and 55, and accompanying text.

There is no known risk to your baby from monitoring with the pulse oximeters used for this study. The possible risk of skin breakdown at the site will be minimized by your baby’s nurse moving the oximeter to another arm or leg a couple of times a day.¹⁰

OHRP found that these descriptions “failed to include or adequately address” the requirement that: “A description of any reasonably foreseeable risks and discomforts” be included as required by federal regulation 46.116(a)(2).¹¹ OHRP concluded that while each of the two groups in the study was within the 85-95% range of standard of care oxygen levels, the higher range (91-95%) and the lower range (85-89%) each differed from the usual standard of care.¹² Moreover, OHRP found that the purpose of the study itself was to determine if one of the two ranges was superior in terms not only of ROP, but also “neurological development and possibly death.”¹³ On this basis, OHRP required UAB to “provide a plan that the IRB will use to ensure that approved informed consent documents include and adequately address the basic elements of consent as required by HHS regulations 45 CFR 46.116(a).”¹⁴ In a letter of its own, UAB quickly (and reasonably) responded that it had “revised the sample consent form provided to

¹⁰. UAB CONSENT FORM FOR SUPPORT in EXTREMELY LOW BIRTH WEIGHT INFANTS 3-4 (Oct. 1, 2004), available at http://www.citizen.org/documents/support-study-consent-form.pdf [hereinafter UAB CONSENT FORM]. There were 23 different consent forms, one for each center, and they had variations. All forms are available at Public Citizen’s website: http://www.citizen.org/hrq2124. The OHRP action related to the consent form used by the University of Alabama at Birmingham. The “sample consent form” for the SUPPORT study was developed by the University of California, San Diego. That form stated flatly regarding risks: “Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. . . . [E]ach of the 4 possible combinations of treatments is considered by some units to represent their desired approach.” UNIV. OF CAL., SAN DIEGO, SUPPORT MANUAL OF OPERATIONS APPENDIX B: SAMPLE CONSENT FORM, NAT’L INST. FOR CHILD & HUMAN DEV., at B-1 (Jan. 4, 2005), http://www.nichd.nih.gov/about/Documents/Consent_Form_Template.pdf [hereinafter SAMPLE CONSENT FORM]. If you read all of the consent forms together you would get the impression that the most important legal issue in the SUPPORT study was privacy of medical records, and the second most important issue was who was going to pay for the neonatal care of the infant, and any adverse consequences to the infant that required additional care. Informed consent, even in the consent form, seemed to be treated much less seriously than these two issues.

¹¹. Buchanan, supra note 9, at 9.

¹². Id. at 9-10.

¹³. Id. at 9.

¹⁴. Id. at 11.
investigators . . . [adding] to the Risks and Discomforts section to instruct investigators to include the specific risks of all arms even if those procedures fall within the parameters of standard of care."\(^\text{15}\) Checklists of institutional requirements had also been “refined to ensure inclusion of all of the basic elements of consent,” and staff members responsible “ha[d] been reminded that the risks of all study arms must be described in the consent document, even when those arms fall within the parameters of standard of care.”\(^\text{16}\)

Shortly thereafter, the Health Research Group of Public Citizen was asked to investigate the matter further, presumably (but we don’t know) by the same person or persons who filed the original complaint with OHRP. On the basis of their own review, Public Citizen wrote a letter to the Secretary of HHS expressing “serious concern regarding the grossly inadequate corrective actions” OHRP required.\(^\text{17}\) After outlining its own concerns with the consent form, and the lack of action by any of the 23 IRBs in the SUPPORT study, Public Citizen concluded that “the egregious deficiencies in the informed-consent process alone resulted in indefensible, highly unethical research involving vulnerable premature infants.”\(^\text{18}\) Public Citizen asked the Secretary to direct OHRP “to expand its compliance-oversight investigation of SUPPORT” to include the “ethics of the study design” and asked her to issue “a formal apology” to the parents of all 1,316 subjects enrolled in SUPPORT.\(^\text{19}\) Public Citizen also asked the Secretary to initiate an “independent investigation of the HHS system for review and oversight of HHS-funded human subjects research to understand how the system failed so miserably in the case of the SUPPORT study.”\(^\text{20}\)

Initial reactions to Public Citizen’s complaint varied widely, from describing SUPPORT as grossly “unethical,” and the failure to obtain informed consent as “startling and deplorable,” to attacks on OHRP itself as uninformed and off the mark.\(^\text{21}\) The major argument for not disclosing the

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16. Id. at 1-2.


18. Id. at 11 (emphasis added).

19. Id. at 11.

20. Id. at 12; see also infra, note 45 and accompanying text.

21. See e.g., Editorial, An Ethical Breakdown, N.Y. TIMES (Apr. 15, 2013) (“23 academic institutions authorized a research project that failed to meet the most basic standard: providing an informed consent document to parents that accurately described the risks and benefits of the research to be conducted on extremely premature babies. This failure was startling, and deplorable.”).
risks of death and blindness in each arm of the study was that because the oxygen levels used in both arms of the study were within the wide range of oxygen levels currently in use, each arm could be characterized as “standard of care.” Because extremely premature infants could have gotten either high or low oxygen ranges in the non-research, therapeutic setting with their own physicians, the infants, it was argued, experienced no additional risk by being randomized to one or the other arm of the study.\(^\text{22}\)

In early April the New York Times ran a front-page article under the headline “Study of Babies Did Not Disclose Risks, U.S. Finds.”\(^\text{23}\) In the story Richard B. Marchase, vice president for research at the University of Alabama at Birmingham, was quoted as saying that he had already assured OHRP that in the future “we will to the best of our ability let the subjects or their parents know as thoroughly as possible what previous studies suggest in terms of risk,” adding, “[w]e are going to be very sensitive to that going forward as we look at these consent forms.”\(^\text{24}\) An article the next day in the Washington Post quoted a neonatologist at the University of California at San Diego as saying “I don’t have any regrets. Everybody went into this with their best intention. Nobody was trying to deceive anybody.”\(^\text{25}\) In the Post article Marchase added, “[b]ecause all the infants were being treated in the standard of care, investigators agreed that the extent to which risks and benefits were delineated in the consent form was appropriate.”\(^\text{26}\)

22. Echoing the San Diego consent form, SAMPLE CONSENT FORM, supra note 10, the form reads: “Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby.”


24. Id.


26. Brown, supra note 25 (emphasis added). Shortly thereafter, on April 17, 2013, a class action lawsuit was filed against the Director, Chair, and individual members of the IRB of the University of Alabama, as well as the SUPPORT researchers, alleging, among other things, that named infants in the study “have suffered permanent neurological and vision issues” because of the study’s unethical design and the failure of the consent document to disclose the risks “with respect to which arm of the study their infants were randomized into.” Looney v. Moore, No. 2:13-CV-00733, WL 1910388, ¶ 6, ¶ 9 (N. D. Ala. filed Apr. 17, 2013). Concern about potential liability from suits like this one is likely to have influenced at least some of the commentators who have spoken and written about the ethics of the SUPPORT study. Proving that either the study design or the deficiencies in consent caused injury to any particular newborn is the major hurdle in this
After the SUPPORT study had been published in the *New England Journal of Medicine*, Editor-in-Chief Dr. Jeffrey Drazen quickly coauthored a strong editorial in favor of conducting research with extremely premature infants in general, and defended the SUPPORT study specifically. He and his coauthors expressed disappointment in OHRP’s conclusion that the risks to the neonates had not been stated in the consent form, stating that the finding:

[D]oes not take into account either the extent of clinical equipoise at the time the study was initiated and conducted or that the consent form, viewed in its entirety, addressed the prevalent knowledge fairly and reasonably. At the time . . . 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 . . . [a risk] later uncovered by the trial itself.

Dr. Drazen’s editorial concluded that OHRP’s investigation:

[H]as had the effect of damaging the reputation of investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice. . . .We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.

The same issue of the *Journal* also contained a Perspectives piece by two bioethicists, David Magnus and Arthur Caplan, and a letter from the SUPPORT researchers defending their consent form:

Our consent forms were conscientiously drafted according to the Code of Federal Regulations and were based on the best available evidence. We provided parents with the information known at the time, which did not indicate an increased risk of death resulting from assignment to either treatment group. We have adhered to

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lawsuit. An alternative theory for failure to obtain informed consent is that this is a dignitary harm that warrants compensation. See, e.g., Peter Aronson, *A Medical Indignity*, NAT’L L. J., Mar. 27, 2000, at A1, A8 (discussing a $3.8 million settlement in a case in which mostly indigent and non-English speaking pregnant women were recruited into a research trial involving multiple amniocenteses without their informed consent).


28. Id. at 1930.

29. Id.

the highest ethical principles, and we will continue to work to ensure that known potential risks are described in our consent forms.\footnote{Magnus and Caplan characterized OHRP’s insistence on including the risk of death in the consent form as factually wrong: “asking that research be described as riskier than it really is and . . . suggesting that the parents were}

Magnus and Caplan characterized OHRP’s insistence on including the risk of death in the consent form as factually wrong: “asking that research be described as riskier than it really is and . . . suggesting that the parents were
duped into enrolling their frail infants in dangerous research.”32 They rejected OHRP’s conclusion because they believe that both arms of the SUPPORT study can be characterized as “standard treatment” (and thus did not increase risk of death or blindness to the infant). In any event, they continued, death is a well-understood risk with premature infants: all this is “taking place in a clinical context in which parents understand that the standard treatments may be unsuccessful and that there is a grave risk of death.”33

The Director of the National Institutes of Health (“NIH”), Francis Collins, and coauthors also defended the SUPPORT study in the Journal with a short piece entitled “In Support of SUPPORT.” Collins rejected the suggestion that either arm of the SUPPORT study could objectively be thought to create an increased risk of death, writing:

The more recent studies [after 2000] showed no increased risk of death or neurodevelopment impairment at saturation levels as low as 70%. Given these data, the investigators had no reason to foresee that infants in one study group would have a higher risk of death than would those in the other group . . . The increased risk of death was 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 it would have been unethical to conduct the study.34

The writers noted that the controversy “has alarmed some of the parents of infants who were in the study, confused the biomedical research community, and befuddled IRBs.”35 Because of this alarm, the NIH writers announced that HHS had decided to engage in a “national dialogue with the research, advocacy, and ethics communities on how best to respect and protect participants in research studies conducted within the standard of care and how to define ‘reasonably foreseeable risks’ in this setting.”36 Actions included putting the compliance action against the University of Alabama on hold, and conducting a public hearing on “standard of care research” with the goal of producing “appropriate guidance” on this subject.37

32. Magnus & Caplan, supra note 30 at 1865.
33. Id. (emphasis added).
35. Id. at 2351.
36. Id.
37. Id.
A. Dueling Ethicists

The consent dispute engaged two conflicting groups of bioethicists, each of which published their opinions in the *New England Journal of Medicine.* Supporters of the SUPPORT study published first. Benjamin Wilfond and colleagues urged OHRP to withdraw its risk of death finding because, they argued, OHRP’s conclusion that either of the two arms of SUPPORT’s “routinely used oxygen-saturation levels exposed subjects to additional risk (above the risks of routine clinical treatment) is not supported by the evidence . . . [and] is without substantive merit and overreaches.” Their primary concern was not for the research subjects or their parents, but for the researchers and their institutions: “Allowing the decision to stand would be unfair to the investigators and institutions involved in SUPPORT.” On the other hand, they did acknowledge that “the permission [sic] forms could have been improved,” and that “the consent process for clinical research can no doubt be improved.”

In response, a competing group of bioethicists and physicians wrote in support of OHRP’s risk determination, which they described as “justified,” and not an “overreach.” Ruth Macklin and colleagues argued that no matter how important the study, “the consent process must be clear enough to enable informed decision making.” The signatories found the consent forms seriously deficient because: none of them “specifically mentioned death as a possible risk of the oxygen interventions in the study;” they lacked an adequate description of alternatives; they did not describe the use of modified oximeters; and they did not explain the differences between the research and clinical care. The group also rejected the argument that,

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40. *Id.*
41. *Id.* (“Although we acknowledge that the permission forms [sic] could have been improved, we disagree that the random assignment of infants to a high oxygen-saturation level or a low oxygen-saturation level imposed additional risks that the investigators failed to disclose.”).
42. Macklin et al., *supra* note 38 (responding ethicists’ letter signed by physicians, bioethicists, lawyers, and scholars in allied fields). See also Ruth Macklin & Lois Shepherd, *Informed Consent and Standard of Care: What Must be Disclosed,* 13 AM. J. BIOETHICS 9, 13 (2013) (“Researchers are of course well intentioned...But it is the doctors, and not the researchers, who have a fiduciary obligation and long-standing ethic to pursue the patient’s best interests above all other considerations.”).
43. Macklin et al., *supra* note 38.
44. *Id.*
because both arms of the study were within the “standard of care,” there was no additional risk to the subjects:

The potential risks and benefits of being in the study could not be said to be the same as the potential risks and benefits of receiving care outside the study, in settings in which infants were not randomly assigned and held to oxygen levels at either end of a wide range of oxygen-saturation levels generally considered to be safe. Nor could the risks and benefits be said to be the same in the two groups of the study. Of course, the outcomes were not known ahead of time, but a potential differential in the risks that were being tracked (death, retinopathy of prematurity, and neurologic impairment) was reasonably foreseeable, since determining differential risk was the very purpose of the study.45

In a separate analysis published in the British Medical Journal, bioethicists Jon Merz and Nancy King noted that in the design of the study, the primary outcome across the two arms “was comparison of death or retinopathy of prematurity” (‘ROP’).46 But, they argued, while combining these two outcomes into one may help arrive at a statistically significant finding, it comingles two outcomes that are not comparable.47 In their words, “death is a much, much more serious outcome than ROP. Indeed, many parents may simply be unwilling to take any increased chance of death just to avoid ROP—another reason the tradeoff should have been disclosed to parents.”48

B. The Public Meeting

The public meeting on SUPPORT and OHRP’s compliance action was held on August 28, 2013, and was attended by more than 200 people.49 The written presentations are available on the HHS website, the oral presentations are all posted on YouTube, and a transcript of the remarks is

45. Id. (emphasis added).
47. Id.
48. Id.
available. Many who had previously written on the dispute spoke, including Drs. Michael Carome and Sidney Wolfe of Public Citizen, and New England Journal of Medicine Editor-in-Chief Dr. Jeffrey Drazen. The panel which presided over the hearing, and asked questions, was composed of representatives of three agencies within the HHS: OHRP (represented by its Director, Jeffrey Minikoff), the NIH (represented by Kathy Hudson, Deputy Director for Science Outreach and Policy) and the Food and Drug Administration (“FDA”, represented by Robert Temple, Deputy Center Director for Clinical Science, Center for Drug Evaluation and Research). The hearing can be fairly characterized, we think, as mostly noncontroversial in that most speakers made points that either were not in dispute, or that were irrelevant to the controversy over the quality and content of the SUPPORT study’s consent forms. No one, for example, contended that comparative effectiveness research should be abandoned, or that all clinical care should be characterized as research, or that the distinction between clinical care and research should be abolished (although some speakers did contend that almost all of what physicians do is not evidence-based, and that physicians really do routinely make many “random” treatment decisions).

50. Id.

51. Id.

52. Chris Feudtner, Mark Schreiner & John D. Lantos, Risks (and Benefits) in Comparative Effectiveness Research Trials, 369 NEW ENG. J. MED. 892-94 (2013); David Magnus, Comments at the OHRP Public Meeting (Aug. 28, 2013). This view has some support in the bioethics literature. See, e.g., Samuel Gorovitz & Alasdair Macintyre, Toward a Theory of Medical Fallibility, HASTINGS CENTER REP., 13, 20 (1975) ("every therapeutic intervention is an experiment in regard to the well-being of that particular patient."); and A.C. Ivy, The History and Ethics of the Use of Human Subjects in Medical Experiments, 108 SCIENCE 1 (1948) ("we frequently forget to recall the fact that a patient is a voluntary experimental subject of the physician. The physician practices medicine today, and because the response of different patients to the same therapy will always vary to some extent, the physicians will always practice medicine on his patient." [emphasis in original]). Both of these comments illustrate the inherent tension between the value of generalizable medical/scientific knowledge, and the fact that each patient is an individual who may not react like the “average” patient to any given intervention. That the patient, and the subject, are unique individuals with their own values and interests is, of course, the primary reason physicians and researchers alike are obligated to obtain their informed consent before treating them or conducting research on them. These views are well-summarized by Jay Katz in a 1993 article: “Physician-investigators have long maintained that clinical research and therapy, more often than not, are indistinguishable; that the drugs or therapies they subject to scientific study frequently are, or could be, proffered to patients in therapeutic settings; and that the only difference between their scientific endeavors and clinical practice resides in the objective
A few, including the Association of American Medical Colleges, argued that the sky really was falling, and that the reaction to SUPPORT would lead physicians to abandon research altogether if they had to disclose the risks of standard of care treatments to patients. In their words:

Even the most dedicated physician scientist may think twice before heading into the debris left by the public condemnation of the SUPPORT study, which called into question the ethics of the government and the investigators. In the end, that hesitation could bring comparative effectiveness research to a grinding halt, leaving physicians in the untenable position of taking a reasonable guess, instead of ensuring that all patients receive treatment based on the best possible evidence.\footnote{Id.}  

This is an overreaction because the OHRP letter did not call “into question the ethics of the government and the investigators” at all.\footnote{Id.} The letter was addressed to an institutional official, and noted deficiencies in the consent form approved by the IRB that was under the official’s jurisdiction. The exclusive target of OHRP was the institution’s failure to write a complete consent form for SUPPORT. This failure does, however, suggest, as Public Citizen noted in its own letter, that a central issue that remains to be addressed is how 23 IRBs could have done such a poor job in reviewing and approving the deficient consent forms for the SUPPORT study. Nonetheless this issue got almost no comments at the public meeting.\footnote{Id.}
The hearing did, however, underline three points that had not previously been emphasized which should help HHS officials provide institutions and IRBs with additional guidance going forward: (1) Studies that examine “titrated” treatments by comparing extremes of existing treatment levels are unlikely to provide any clinically useful information unless they have a control group that represents actual practice (aka “standard of care”); (2) SUPPORT researchers who were experienced neonatologists had to know prior to beginning enrollment in the SUPPORT study that a reasonable risk of being in the lower range of oxygen was an increased risk of death; and (3) At least some parents agreed to participate in the SUPPORT study because they did not understand the study, its risks, or that they would not have a physician making decisions based on their best medical judgment.

The first point, that determining what titrated treatment is best by comparing the extremes of currently used treatment (here, the oxygen levels), is unlikely to provide clinically useful information unless a control group is included in the design. This point was well explained by two clinicians at the National Institutes of Health, Drs. Charles Natanson and Robert Danner. Natanson went even further, under questioning from Temple, describing studies of extremes as “physiology experiments,” and not legitimate human experiments. In his view, they have no real hypothesis and thus don’t qualify as experiments (the notion that one extreme is likely to have different clinical outcomes than the other extreme is, he implied, both obvious and unhelpful, since no one is likely to be treating exclusively at either extreme in the real world of clinical medicine). In this regard, Natanson and Danner raised the bar to include not just informed consent, but whether the design of the study itself meant that the risks to the subjects could not be outweighed by the potential benefits of the research. If so, of course, the research simply could not be done on human beings, informed consent being a necessary but not sufficient justification for research on humans.

66. Id.
67. Charles Natanson, Comments at OHRP Public Meeting, supra note 49.
68. Id.; Robert Danner, Comments at OHRP Public Meeting, supra note 49. See also Katherine J. Deans, Peter C. Minneci, Peter Q. Eichacker & Charles Natanson, Defining The Standard Of Care in Randomized Controlled Trials of Titrated Therapies, 10 CURRENT OP. CRITICAL CARE 579-582 (2004); Charles Natanson, Katherine J. Deans, et al., Randomization in Clinical Trials of Titrated Therapies: Unintended Consequences of Using Fixed Treatment Protocols, 35 CRITICAL CARE MED. 1509-16 (2007).
The second point was made by the only SUPPORT researcher who appeared at the hearing, Dr. Jon Tyson. Tyson repeated the position of some of the SUPPORT study researchers that the reason they did not disclose the possibility of an increased risk of death at the lower level arm of the study was that “based on the best available evidence, the investigators in the trial did not believe that mortality would be increased with reduced or lower saturation levels.” He was pressed on this issue by Temple, who said, among other things, that he found it difficult to accept that no one worried “even a little bit” about the lower oxygen levels, noting that “everything has a dose-response” and wondering why there would be no concern here. Tyson responded that they were at equipoise and that observational data had shown levels as low as 70% were “safe.” He also said that he thought lower levels (85-89%, which he had used in his own practice) would be safe if we could better “adjust the FiO2 to the baby’s needs,” and had “better staffing” in the NICUs to respond quickly when levels got too low. Temple responded by saying he understood that the researchers didn’t think the lower levels increased mortality. Tyson replied, in frustration, that if the study had come out the other way (with mortality increased at the higher levels), Temple (and others) would be criticizing the researchers for not disclosing that risk of death, based on the data obtained from the trial itself. Temple responded, no, that he was just saying that “in areas of uncertainty, maybe [you owe] patients some explication of what the uncertainties are.”

Two parents, who had agreed to have their newborns enrolled in SUPPORT, spoke about what they understood about the study. Shawn Pratt’s daughter, Dagen, who is now 6 years old, was born at 25 weeks, and has cerebral palsy. He said they had been asked to be in many studies, and generally consented to be in those that involved observation, medical record review, and even blood examinations. They had, however, refused to be involved in an acid reflux study because of the risks. As to SUPPORT, Pratt said it “looked good on paper” and that they did not understand that

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59. Jon Tyson, Comments at OHRP Public Meeting, supra note 49.
60. Id.
61. Robert Temple, Comments at OHRP Public Meeting, supra note 49.
62. Jon Tyson, Comments at OHRP Public Meeting, supra note 49.
63. Id.
64. Id.
65. Robert Temple, Comments at OHRP Public Meeting, supra note 49.
there would be any risks to his daughter from being in the study, and that the “risks and intent of the study were not clear.” He ended by saying, “[t]ell me that the SUPPORT Study did not hurt Dagen [his daughter] any way.” He asked, “would you place your own medically fragile premature child into the SUPPORT study?” Under questioning, his wife noted that this was a particularly vulnerable time for the parents and that more needs to be done to make sure the parents understand what is being asked of them and their child.

Sharissa Cook’s son, Dreshan Collins, was born at 25 weeks. She said that there was a general lack of information, that she now feels she was “taken advantage of and I feel responsible for my child’s participation in this study.” She said she did not understand the study at all, and thought it was designed to give her and her son “support” in this very difficult time. Temple asked her directly if she knew at the time that she was being asked to put her son in an experiment, to which she replied:

No sir. I was under the impression that this was more of a support group, I guess I should say, where they would be holding our hand throughout the process to let us know if there were any types of delays or anything that we could do since they were premature babies. You know, it was my first child. So I was under the impression that this was more of more support and this is something that could be beneficial to me as well as my son, because we have someone there to help us along the way.

It is extremely unlikely that these were the only parents of the 1,300 who enrolled their newborns in the study that did not understand the SUPPORT study when they agreed to put their children in it. Merely changing one line in a complicated consent form is not likely to have made much difference. As Ms. Cook put it, parents are very vulnerable when they have an extremely premature infant, and actually need real support. Of course, informed consent is a process, not a form (and it is a noun, not a verb). Is it possible to make the informed consent process for research on extremely

67. Shawn Pratt, Comments OHRP Public Meeting, supra note 49.
68. Id.
69. Carrie Pratt, Comments at OHRP Public Meeting, supra note 49. At a press conference, held during the lunch break, Dagen’s mother, Carrie Pratt, asked reporters: “Why is omitting information not considered lying? We were told they would give her the best care every day.” Lauran Neergaard, Baby Study Spurs Ethics Debate Over Research Risks, ASSOCIATED PRESS (Aug. 29, 2013), available at http://bigstory.ap.org/article/preemie-study-sparks-debate-over-risks-research.
70. Sharissa Cook, Comments at OHRP Public Meeting, supra note 49.
71. Id.
72. Id.
premature infants better? The editors of perhaps the leading general science journal in the world, Nature, usefully asked readers to put themselves in the position of parents asked to enroll their newborn child in SUPPORT in words we agree with, and believe most physician-researchers agree with as well:

Put yourself in the position of a parent with an extremely premature infant. Would you make the decision to enroll your child in the trial if the consent form stated in simple language that babies assigned to one group were more likely to go blind, and that those in the other group were at higher risk of getting neurodevelopmental disabilities? Equally, would you decide to enroll if the form spelled out that, if you do not take part, your own physician and institution might keep your infant in the middle of the range, trying to avoid either outcome? Perhaps you might, but you would do so with full knowledge of the attendant risks. The parents in this case could not do so...

No matter the thorniness of the issues raised [at the OHRP Public Hearing] research is still research in whatever context, and the duty to protect human subjects must remain paramount.73

What can be done to better protect extremely premature infants and their parents is, as the Nature editors concede, a “thorny” issue?74 The most important step, we think, is to take informed consent seriously—in both the research and treatment contexts—and to understand that having a personal physician whose primary interest is your child’s welfare (rather than following a research protocol) is extraordinarily important to most sick people, and most parents of sick infants.

C. Informed Consent and “Standard of Care” Treatment

There really is only one argument put forward for not telling parents about the potential risk of death from volunteering their extremely premature baby to the SUPPORT study: both arms of the study were within the range of oxygen saturation used in clinical medicine at some hospitals, so they could both be seen as “standard of care” (somewhere), and thus being randomly assigned to one or the other arm did not increase the risk of death to the baby. This argument cannot be taken seriously for a number of reasons. First, as already suggested, there really is a difference between research and treatment, and the phrase “standard of care research” is an oxymoron that, much like “therapeutic research,” seems to be designed and used primarily

73. Editorial, Subject to Question: Even When Conducting Clinical Trials to Study Widely Used Therapies, Researchers Must Ensure That They Disclose the Full Risks to Patients, 500 Nature 377 (2013).
74. Id.
to blur and confuse the differences between research and treatment. The primary difference is that in treatment a patient has a physician who is bound by a fiduciary duty to act in the patient’s best interests (of course, with the patient’s consent). In contrast, in research the researcher is duty-bound to follow the research protocol and may not deviate from it, even if the researcher believes a deviation is in the best medical interest of the subject (of course, if the subject is in danger, the researcher has an obligation to end the subject’s participation in the research). Second, following standard of care does not eliminate the legal requirement to obtain informed consent. Informed consent is required for both research and treatment. Third, “standard of care” has a variety of meanings that make its use in the research context confusing and counterproductive. And, finally, no one was actually using either of the SUPPORT study’s two arms in clinical practice—as few, if any, physicians were practicing exclusively at either extreme of the current-practice clinical range, and none were using a pulse oximeter that gave inaccurate readings, or ignoring clinical signs that would cause “standard of care” providers to change the oxygen saturation levels in their newborn patients.

Standard of care is a concept most often seen in medical malpractice cases in which the plaintiff has the burden of proof. Specifically, the plaintiff must prove that the defendant physician did not act in accordance with what a “reasonably prudent physician would do in the same or similar circumstances.” This is simply a definition of the legal duty of a physician, i.e. to act in a manner consistent with the medical standard of care. Two points should be obvious. First, as a series of courts have ruled, the standard of care takes informed consent for granted as a legal requirement, regardless of what physicians usually or “customarily” do. Physicians have a legal duty to obtain voluntary, competent, informed and understanding consent before doing any procedure on a patient that has material risks. As the California Supreme Court put it in 1972 in Cobbs v. Grant, physicians are obligated by law, because of the fiduciary nature of the doctor-patient relationship, to disclose all material risks of a proposed therapy. 


76. Cobbs v. Grant, 502 P.2d 1 (Cal. 1972); Truman v. Thomas, 611 P.2d 902 (Cal. 1980) (in bank); Moore v. Regents of Univ. of Cal., 793 P.2d 479 (Cal. 1990) (in bank). See generally George J. Annas, The Rights of Patients ch. 6 (3d ed. 2004) and Katz, Human Experimentation, supra note 2, at 13-14 (“[T]he doctrine of informed consent, as currently articulated, imposes similar disclosure and consent obligations for therapy and research, with the only difference being that for research the informed
“Material” risks always include death and permanent disability, but also include any risks that might lead a reasonable patient to refuse the proposed treatment. It is the patient’s life and future that is at stake, and the patient has a legal right to rely on the physician to disclose information that affects their decision to put their life and future in the physician’s hands. The view that informed consent is only required for research and not for treatment can only be held by someone who can reasonably be described as “legally blind.” Research and treatment are different. One recurring difference in SUPPORT, for example, is that the use of pulse oximeters set to give inaccurate readings can be acceptable in a research protocol, but would be malpractice per se in the clinical care setting. In terms of informed consent, the doctrine applies to both, but because the research-subject relationship lacks a fiduciary basis, informed consent is more ritualistic and procedurally-based in research than in treatment: subjects are required to be given and to sign a written consent form, and the consent form itself must be approved by an IRB. On the other hand, SUPPORT researchers are likely correct in observing that informed consent in the NICU is more elaborate and taken more seriously by researchers than clinicians. But this is a problem with implementing the doctrine of informed consent, and should not be used as an excuse to abandon it.

From the legal perspective, there is not much new in the SUPPORT discussion. All of the issues raised by the SUPPORT study, and the reactions to it, were the subject of litigation more than 30 years ago, litigation which itself was based on events that transpired in 1953. As summarized by a New York appeals court, the facts of the case are straightforward. The plaintiff, Daniel Burton, was born six weeks premature on July 3, 1953, weighing 3 lbs. He was transferred the next day.
to New York Hospital, which had the city’s only premature nursery care center. At the time, about half of the infants of his size died, and many survivors had either brain damage or blindness. The blindness is caused by retrolental fibroplasia (“RLF”), now called retinopathy of prematurity (“ROP”), which a “respected minority” of the medical profession believed was caused by too much oxygen. As the court described the physicians’ dilemma in 1953:

The medical profession was confronted with a terrible dilemma—the antidote to two problems, death and brain damage, appeared to be the cause of another, blindness. One court, commenting on the perplexity of the problem, spoke of the anxiety of those physicians who “tried to steer their tiny patients between the Scylla of blindness and the Charybdis of brain damage.”79

Just two days before the plaintiff’s birth, a research study on the effects of oxygen on blindness (“Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen”) was commenced. The study concluded, in 1956, that prolonged use of oxygen was the critical factor in developing blindness, and that curtailment of oxygen after 48 hours to clinical need decreased the incidence of blindness without increasing the risk of death or brain damage. Although the New York Hospital had done its own study that demonstrated that prolonged oxygen exposure may be linked to blindness, it joined the new Cooperative Study about the time Daniel was admitted. Daniel’s condition on admission was “good” with no abnormalities, other than his prematurity. From the time of his birth, Daniel had been getting four liters of oxygen continuously. His admitting physician, a resident named Lawrence Ross, directed that oxygen be continued at its current level, but, aware of the relationship between oxygen and blindness, ordered that oxygen be “reduced as tolerated.”80

At trial, Ross testified that this order was “good medical practice and in accordance with my judgment.”81 The medical records indicated that the oxygen concentration was reduced (from 35% to 30%) in compliance with the order, and the baby was doing well. Two days later, on instruction from the chair of the pediatric department (identified by the court as “Dr. Levine”), pediatrician Mary Engle, entered Daniel into the Cooperative Study. He was randomized into the 50% or greater oxygen concentration arm (one third were placed in this arm, the other two-thirds in lower oxygen concentration arms). Neither Dr. Ross nor the parents were consulted. As a result of being in the study, Daniel’s oxygen levels over the next 28 days

80. Id. at 220.
81. Id.
went to as high as 82%, which Engle testified was within “routine practice,” and consistent with New York Hospital’s manual on the “Management of Premature Infants.”

Daniel’s eyes were examined by specialists on six different occasions (three times while he was in the 28 day high oxygen study, and three times in the following month), documenting a slow deterioration in vision, including bleeding, that ended in his total blindness. In 1975, Daniel brought suit against the hospital, the resident (Ross), and the pediatrician (Engle) for medical malpractice and failure to obtain informed consent before putting him in an increased oxygen environment. The jury found the hospital and Dr. Engle liable on both counts. Dr. Ross was absolved from liability for negligence, but found liable for failure to obtain informed consent.

The hospital and the two physicians appealed. Their first defense was that their actions were all within the standard of care. The court decided that the trial judge was correct to put the following issues to the jury:

Whether defendants followed sound medical practice in 1953 in permitting plaintiff to be exposed to an increased oxygen environment for a prolonged period, even if it was common practice at the time, when they were aware of the possibility that RLF [blindness] might result. Ancillary to that question was whether, even if defendants exercised proper medical judgment, they should have informed plaintiff’s parents of the risks involved, and obtained their consent.  

The appeals court concluded that the jury’s verdict was supported by the evidence with regard to Engle and the hospital, but reversed the verdict against Ross “who did not order the increase in oxygen, and whose own order to reduce oxygen was countermanded.” As to Engle, the court ruled that her actions could not be characterized as “acceptable medical practice” because in making the decision to enroll Daniel in the research, and to randomly assign him to the high oxygen arm, she was exercising no medical judgment at all, and in fact never even examined Daniel, who had been doing well. “It seems reasonably clear that Dr. Engle’s order to increase the oxygen supply was an administrative judgment, based upon a random allocation of babies into one of two groups for monitoring as part of the Cooperative Study.”

There are many similarities between the Burton case and the SUPPORT controversy. The parents in Burton testified that they were asked to sign what is now known as a “general” consent form, authorizing “the doctors of

82. *Id.* at 222 (emphasis added).
83. *Id.*
84. *Id.* at 223.
the New York Hospital to give such treatment and medication to my son which in their judgment becomes necessary while he is a patient in New York Hospital.” 85  The form also contained language waiving all claims to prior notification of any treatment, and contained no language about any risks. The defendants argued that there was no duty to obtain informed consent in New York until 1965, and that in 1953 it was the hospital’s practice to have the resident [Dr. Ross in this case] inform a patient’s parents of all the risks involved and the options available before any patient was put into an experimental study (Dr. Ross had no recollection of so informing the parents). 86

The court had little difficulty finding a duty on the part of physicians to obtain informed consent to any procedure involving “unwarranted risks.” In the court’s words, “doctors were never free to expose their patients to unwarranted risks without first obtaining their consent.” 87 Quoting a 1914 New York case, the court continued: “Every human being of adult years and sound mind has a right to determine what shall be done with his own body.” 88 As to the language of a 1957 case sometimes (incorrectly) identified as the first “informed consent” case in the U.S., the court noted that the case merely recognized formally a duty that had always existed. 89

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85. Id. at 225.
86. Id. at 225. Of course there were no IRBs in 1953, and an IRB may well have prevented Burton’s enrollment in the study. Nonetheless, a consensus seems to be growing that IRBs have become ineffective at protecting research subjects. As Professor George Smith has put it, “In assessing the effectiveness of the nationwide system for protecting the rights and welfare of human research subjects, a pervasive sense of crisis is found. Government studies show conclusively that IRBs review far too many protocols within an accelerated time frame, lack adequate resources to conduct careful reviews, and do not have sufficient levels of expertise within their membership ranks in order to complete their evaluations. The whole review process has been found to be too tilted in favor of the researcher and the institutional interests over those of human subject protection.” GEORGE P. SMITH II, DISTRIBUTIVE JUSTICE AND THE NEW MEDICINE 115 (2008).
88. Id. (citing Schloendorff v. Society of New York Hosp., 105 N.E. 92 (N.Y. 1914)).
89. Burton, 88 A.D.2d at 226 (citing Salgo v. Leland Stanford Jr. Univ. Bd. Trustees, 317 P.2d 170, 154 Cal.App.2d 560 (1957)). Consent has a long history in the law, although the penchant to put adjectives in front of this noun is more recent and includes not only informed consent, but other neologisms such as broad consent, deferred consent, tiered consent, and implied consent. The Nuremberg Code itself used the adjectives voluntary, competent, informed, and understanding (1947). See, e.g., George J. Annas, DOCTORS, PATIENTS, AND LAWYERS—TWO CENTURIES OF HEALTH LAW, 367 NEW ENG. J. MED. 445 (2012). Nor is consent in the research setting a modern invention. Historian-
that court’s words, “a physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment.”\textsuperscript{90} The court concluded that there was such a duty in 1953, and that whether the hospital followed its own consent practices in this case was a question of fact for the jury.\textsuperscript{91} The jury’s verdict was affirmed as to both the hospital and Engle, and reversed as to the resident. The amount of the award, however, was reduced from $2,887,000 to $1,500,000 ([$3,731,000 in 2013 dollars], the original amount having been found “disproportionate” to Daniel’s injuries.

The \textit{Burton} case stands for a number of legal principles directly relevant to the SUPPORT Study and its consent process. First, informed consent is a legal duty that obligates a physician to disclose major risks of both treatment and research. Second, whether characterized as “standard of care,” “common practice,” or “sound medical practice,” the risks of treatment, as well as benefits and alternatives, must be disclosed to the patient so that the patient can make his or her own decision. Third, even when there is a broad spectrum of possible “standard” or “accepted” oxygen levels, physicians are likely to favor one near the center of a normal distribution, and “cannot avail themselves of the shield of accepted medical practice when a number of studies . . . had already indicated that increased oxygen was both unnecessary and dangerous . . . a physician should use his best judgment and whatever superior knowledge skill and intelligence he has.”\textsuperscript{92}

In short, the primary argument against disclosing the risk of death in the SUPPORT study, that because all oxygen levels were within someone’s “standard of care” no new risks were introduced to the patient, is explicitly rejected by this court. The difference between research and treatment is also spelled out: having care determined by a protocol, rather than by your physician’s “best judgment.” The secondary argument, that physicians have no scientific basis for their practices (the reason we need to do research on their practices) so they are simply picking treatments at random (making

\textsuperscript{90} Burton, 88 A.D.2d at 226 (citing Salgo, 154 Cal.App.2d at 578).
\textsuperscript{91} Burton, 88 A.D.2d at 226.
\textsuperscript{92} \textit{Id.} at 223 (citing Toth v Cmty. Hosp. at Glen Cove, 239 N.E.2d 368 (N.Y. 1968)).
explicit randomization no more risky) was also soundly rejected. In the eyes of the law and the public (and, we would guess, an overwhelming number of physicians), it is not only the “gold standard” randomized clinical trial that can provide evidence for treatment decisions, but also the physician’s experience, knowledge, intelligence, and actual examination and care of the patient, including modifying treatment based on how the patient reacts to it.\textsuperscript{93} In fact, the entire movement to expand the research enterprise to include many more forms of clinical trials than the “gold standard” double-blind randomized controlled trial is a recognition of the many limitations of this methodology as well.\textsuperscript{94}

\textbf{D. Consent Near Extremely Premature Delivery}

One issue not directly dealt with by anyone other than the parents who testified at the hearing is the practical issue of obtaining voluntary, competent, informed and understanding consent from a parent for research on her extremely premature baby (not yet born) when that research might increase the risk of death for her baby. This is probably because no one wants to suggest that women become incompetent to consent either simply by being pregnant, or at, or near, term. Nor would we suggest that. Nonetheless, there are issues worth additional exploration raised by the

\textsuperscript{93} For example, it is common for a physician to use a “trial and error” approach, telling a patient, “We’ll try this; if it doesn’t work, we’ll try something else.”

\textsuperscript{94} John P.A. Ioannidis, \textit{Why Most Published Research Findings Are False} 2 PLOS MED. 0696-0701 (2005); see also SUPPORT, supra note 5, and Vinay Prasad, Adam Cifu & John P.A. Ioannidis, \textit{Reversals of Established Medical Practices: Evidence to Abandon Ship}, 307 JAMA 37 (2012); Leigh Anne Olsen & J. Michael McGinnis, \textit{REDESIGNING THE CLINICAL EFFECTIVENESS RESEARCH PARADIGM: INNOVATION AND PRACTICE-BASED APPROACHES} (2010); Paul Basken, \textit{Medical Journals Look Beyond Industry to Study Their Shortcomings}, CHRONICLE OF HIGHER EDUC., (Sept. 13, 2013) (Drummond Rennie, deputy editor of JAMA, noted that the pressure on researchers seeking promotions and building careers, as well as from company sponsorship, “guarantees that the report of a randomized clinical trial becomes an illusion. . . . It shimmers between a serious scientific report and, ‘Now a word from our sponsor.’”). In SUPPORT the goal was to perform a “definitive medical trial” to determine “what is safe and effective oxygenation” for extremely premature infants. Cole et al, \textit{supra} note 5 at 1415-16. There is little, if any, evidence that this goal was reached. A meta-analysis of all five trials (SUPPORT plus the trials in the UK, New Zealand, Canada and Australia), will not be available until 2014. There is some hope that the 5,230 sample size which composes all participants will be able to answer the question: Does targeting a lower oxygen saturation range in extremely premature infants from birth or soon after, increase or decrease the composite outcome of death or major disability in survivors by 4% or more? Lisa Askie et al., \textit{NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration Study Protocol}, 11 BMC PEDIATRICS 6, 9 (2011).
SUPPORT study. For example, a study done of some of the consent processes actually used in the SUPPORT study concluded that obtaining consent from women at risk of a premature delivery within the 24-28 week window of the study “was very inefficient and costly and biased the trial enrollment.”95 Other findings included that “only 19% of the mothers who were screened delivered infants who were subsequently enrolled in the study” (five families had to be screened for every infant enrolled), and consent usually took between 30 and 60 minutes to obtain.96 This seemed like a long time to the researchers, but strikes us as a very short period of time to explain SUPPORT.


Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . The aim of this study is to determine, within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%), whether targeting the lower end of this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BDP) problems without increasing mortality or neurodevelopmental disability,” and nonetheless got a better enrollment rate. BOOST-NZ consent form, personal communication from Brian Darlow, principal investigator of BOOST-NZ, July 2005.

Another aspect of the SUPPORT study that has gotten little attention, but deserves more, is the racial composition of the 1,300 infants—approximately 40% of whom were black. This underlines the issue of racial disparities in both medicine and society, as it suggests that extreme prematurity is more prevalent in the black population than in the white population. This suggests, we think, that at least some of these mothers lacked good prenatal care, adequate nutrition, and education compared to the nonblack mothers of premature infants. This is one reason why one of us (George Annas) suggested at the August 28 public hearing that “The problem of extreme prematurity will not be solved in the Neonatal ICU.”

96. Id. at e217. In the SUPPORT study, only 26.1% of the mothers who gave consent ultimately delivered an infant within the study’s gestational age window.
On the other hand, SUPPORT did have a very high rate of refusals, which speaks well of those tasked with obtaining informed consent, and these refusals were in a context that did not discuss the potential increase in the risk of death from the study. To obtain 1,316 infants to randomize, 3,546 infants were assessed for eligibility, of which 2,230 were excluded for some reason, including 699 eligible parents from whom consent was not sought, 344 whose parent or guardian was not available, and 748 who declined to have their infants enrolled in the study. The 748 number is an exceptionally large number of consent refusers—more than a third of the combined number of those who gave consent with those who refused.97

Pregnancy and childbirth are unique experiences, and there is no good medical analogy. When a pregnant patient is admitted to the hospital to give birth she is focused on the two specific purposes of her visit: treatment that

97. Id. Some of the items from the UAB protocol under “14. Consent Form Process” include:

All attempts will be made to allow parents 24 hours to make a decision. If, however, a patient is admitted in active labor or the decision is made by the OB to deliver by cesarean section sooner than expected then it is possible that some consents will be obtained in less than 24 hours. . . . Once a mother has been identified, research personnel will visit her room and explain the study. . . . A significant number of the mothers of infants who are born preterm at University Hospital are under 19 years of age. Because this is a low risk study standard therapies [sic] we would like to obtain consent from these mothers allowing their infants to participate in the study. Because the State of Alabama declares a woman who has delivered an infant to be an emancipated minor, this mother, regardless of age, is the legally authorized representative. [sic] She or the father of the infant (if married) are the only legally authorized persons who may consent for the infant. It is our standard practice to determine the mother’s ability to understand the study purpose, procedures, long-term ramifications, and he and her baby’s rights. If the research personnel determine that the mother and/or father are not capable of understanding the study at his level, they will not be asked to participate based on their inability to understand and make an informed decision regardless of age or maturity level. Additionally, it is our practice when obtaining consent from minors to attempt to have the legal authorized person or representative of the minor (baby’s mother) present during the consent process and sign as witness if she/he is available.

All of this material is in italics and is also underlined. If you were confused reading it, it is likely that the research personnel responsible for obtaining consent were as well. The title of this subsection of the protocol is also a newly-minted phrase that we haven’t seen elsewhere that conflates the consent form with the consent process: “Consent Form Process.” Of course, it also underlines the theory of SUPPORT, that it is simply comparing “low risk standard therapies,” although the word “study” is inserted before “standard” in this part of the protocol.
will enable her child to be born healthy, and treatment that will enable her to go through labor and delivery safely. Information provided to pregnant patients admitted for labor and delivery includes information on many things presented in a fairly succinct way. Typical consent forms, for example, describe tests such as blood tests or fetal monitoring, the types of pain relief available during labor, what to expect if a cesarean delivery is necessary, and rare complications. Because childbirth is the most common occurrence in medicine (with approximately 4 million births a year in the U.S.), there are pretty standard responses to most problems childbirth presents, and there may be limited options. In this context, the right to refuse treatment (and of course, the right to refuse to enroll one’s child in research) may be the most important tool to exercise autonomy that a woman has. Of course, informed consent is not a form; the form is (or at least should be) simply some evidence that the information it contains was discussed with the patient, and the patient agreed (or refused to agree) to the proposed course of treatment.98

Pregnancy is also unique in that the pregnant patient may be required to consider interventions her care team recommends for her health which could negatively impact her fetus. There are also considerations in the reverse—circumstances when the fetus’ best care could involve increased risks to the mother. One example is an unplanned cesarean section birth. Generally, the risk the surgery poses to the pregnant patient’s health is outweighed by the benefit to the fetus of not delaying the birth. However, even in this extreme situation, the pregnant patient has the right to refuse a cesarean section, a right both courts and the American College of Obstetricians and Gynecologists strongly support.99 It would, of course, be paradoxical if the pregnant patient had fewer rights to information and decision-making regarding research on her soon-to-be baby. Because she is the decision maker for herself and her soon-to-be baby, both the law and ethics requires that she be provided with all the material information she needs to make decisions, including any risks of death she or her infant might have.

SUPPORT is, of course, not the only research project ever conducted where consent is sought from a pregnant woman shortly before birth, as Shawn Pratt’s testimony made clear.100 The major barrier to informed consent is not a form; the form is (or at least should be) simply some evidence that the information it contains was discussed with the patient, and the patient agreed (or refused to agree) to the proposed course of treatment.98

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98. George Annas, Remarks at the OHRP Public Meeting, supra note 49.
99. Id. One survey of mothers showed guilt as a predominant emotion when the baby was born premature, while none of the mothers surveyed who had delivered full term but very small babies, expressed guilt. ALBERT R. JONSEN & MICHAEL J. GARLAND, ETHICS OF NEWBORN INTENSIVE CARE 58-59 (1976) (citing David M. Kaplan & Edward A. Mason, Maternal Reactions to Premature Birth as an Acute Emotional Disorder, 30 AM. J. OF ORTHOPSYCHIATRY 539-52 (1960))
100. Shawn Pratt, Comments at the OHRP Public Meeting, supra note 49. The Pratts were asked to consent to a number of studies on their daughter, and did agree to many
consent in this setting is that the pregnant patient is being asked to absorb the possible risks to herself and her baby associated with the proposed research, i.e. she is being asked to consent to something in the future without being able to know the condition her baby will be in at birth. Her major concern is for the health of her baby—but this may not be knowable until the baby is actually born. And it is the baby she is signing up for research, not herself. In the SUPPORT study, consent was being sought when the pregnant patient was being admitted for what would most likely be a pre-term birth within a specific period of gestational age set by the research protocol, but not if the patient was in active labor. This caveat is important because it suggests that the researchers were attempting to approach women whose infants (once born) would be likely to be within the research protocols under circumstances that would allow the pregnant patient to absorb enough information to be reasonably informed when deciding whether or not to consent to having their soon to be born infant involved in a research study.

Neonatologist April Dworetz has described her own experiences treating extremely premature infants and her interactions with the parents of those infants – the “surrogate” decision-makers. She has underlined the lack of counseling and education parents at high risk of having an extremely premature infant receive in our medical system. Many parents have no idea of the extreme interventions and suffering that a 20-something week old infant can undergo simply to keep them alive in a NICU. Although Dr. Dworetz was writing about parental consent for treatment (including whether or not to resuscitate an extremely premature infant who is not that involved mostly an examination of her medical records, or limited blood draws and analysis. Examples of other studies, not directly related to SUPPORT, include: research on the relationship between vitamin C and D supplements and hypertensive disorders, research on the relationship between antibiotic treatment for pregnant women with asymptomatic bacterial vaginosis and preterm delivery, research on the relationship between magnesium sulfate and preventing cerebral palsy, and research on the relationship between progesterone and preventing preterm birth. U.S. Dep’t of Health & Human Servs., Enrolling Pregnant Women: Issues in Clinical Research Forum Transcript 13, 72 (Oct. 18, 2010) (quoting Alan E. Guttmacher and Catherine Y. Spong). One reason for the large number of studies of premature newborns is the high rater of premature births in the US. The US shares its 12% prematurity rate with Kenya, Turkey, Thailand, East Timor and Honduras, and our rate has risen 30 percent since 1981. Donald McNeil, U.S. Fares Badly in Early Births in Global Study, N.Y. TIMES, May 3, 2012, at A1, A4.

breathing at birth), a couple of her points are relevant to the research realm as well. Both parents should always be involved in the decision-making process.\footnote{Id. In contrast, a neonatologist and mother of an extremely premature infant has argued, in the context of SUPPORT, that bioethicists who have criticized the consent process in SUPPORT are self-serving and simply have no idea what goes on in the NICU. She includes ignorance of “how tiny a preterm infant is, how the pulse oximeter is twice as big as she is...how both parents and doctors are obsessed with oxygen saturation numbers.” Because of the many decisions that have to be quickly made in the NICU she recommends replacement of an unworkable informed consent model with an “opt out” model where parents can decide not to receive the information needed to give their informed consent. Annie Janvier, \textit{In Support of SUPPORT: Ignorance and Mistrust can Harm Babies and Families}, 13 AM. J. BIOETHICS 43 (2013).} Parents at high risk of delivering extremely premature infants (or infants with severe congenital deficiencies), should receive counseling about medical alternatives, as well as about values and attitudes towards life. Patients (and research subjects) under similar circumstances have historically been labeled “vulnerable,” but we think it is better to acknowledge that they are a “complex” population.\footnote{See, e.g., Laura Landro, \textit{Hospitals Try to be Child-Friendly as They Face More Young Patients}, WALL ST. J., Nov. 12, 2013, at D1 (“More children are facing painful and invasive procedures, as medical advances have made survival possible for more premature infants . . . Some three million children are considered ‘medically complex’ at present, and their ranks are growing by about 5% a year.”).} This is because the companion to vulnerability is often paternalism, and, as we have said, women do not lose their capacity to make decisions for themselves and their infants simply because they are pregnant. On the other hand, the closer a woman comes to giving birth, especially of an extremely premature infant, the more stress she is likely to be under, and the more time she may need to make a treatment or research decision.

In this regard it would seem that both the consent process and the consent form should be, if anything, clearer and more concise regarding risks of death and bodily disability (for both the woman and her fetus) than for non-pregnant patients. The most important thing for a potential research subject (or here, the parent of a soon to be research subject) to know is “how this research would treat my baby differently than if he or she were simply a patient?” The goal must be to treat the parents or soon-to-be parents with respect and dignity in this process. Because neither the pregnant woman nor her physicians will be able to make a realistic assessment of the health of the baby until it is actually born, perhaps the most important aspect of the consent process in near delivery is the ability to re-visit it after birth. Although we tend to concentrate on obtaining consent itself – and this is reasonable – consideration in this context should be given to upholding the right to withdraw consent at any time as at least as important as providing it
in the first place. That is because the mother is likely to be more informed about the study itself after the baby is born, and she can see her child with (or without) the experimental intervention, and make a more informed decision whether to continue her child in the experiment or not. In this regard, we think it would be helpful to pregnant patients asked to consent to research on their soon-to-be-born infants for OHRP to require institutions and their IRBs to instruct investigators doing studies on premature infants that involve risks of death or disability that:

- Whenever possible, both parents should be included in the consent process regarding use of their infant(s) for research.
- Counseling (independent of information given by the person obtaining consent) should be offered to parents, and should include information about randomization and its consequences (i.e. losing the medical judgment of the treating physician), the interventions that their infant could undergo if the treatment is determined by a research protocol, and how these will differ from the interventions their infant will receive if not enrolled in the research.
- Researchers should use an evaluation technique to test comprehension, such as a questionnaire.
- A second discussion should be held after the infant is born where the risks of the research study are provided again to the parents, and their right to withdraw from the study reiterated.\textsuperscript{105}

HHS should not use the SUPPORT study controversy to weaken existing informed consent regulations, but rather to improve and strengthen them. There is no unique research category called “standard of care research” any more than there is a unique research category of “therapeutic research.” The hold should be removed from OHRP’s reasonable compliance action. Research is research—it should not be confused or conflated with treatment. Potential research subjects need to be told how research differs from treatment, that decisions about care will be made by following a protocol rather than following their physician’s medical judgment, and that there is no obligation to participate in research (although it could benefit others if they do). SUPPORT informs us that we are not doing a very good job of communicating these basic points to potential subjects. On the other hand, there does seem to be general agreement that long and complicated consent forms are not just useless, but counterproductive. They are useless in that

\textsuperscript{105} This is analogous to the procedure recommended in the days when fetal tissue was collected for research from aborted fetuses. The pregnant woman was asked to consent to the collection and use of her fetus’ tissues before the abortion, and then after the abortion she was given an opportunity to change her mind and refuse the tissue collection.
they cannot be understood by most prospective research subjects, and counterproductive because their length alone can make it appear to potential subjects that researchers are providing all the relevant information that they have when this may not be true.

An additional strategy to protect and inform research subjects that HHS should adopt is a radical simplification of existing consent forms. We think they should be reduced to no more than one page. Alternatively, a new, one page cover sheet could be used with the current consent forms retained as an attachment. This proposal applies Atul Gawande’s “checklist” strategy for surgery and childbirth (among other things) to research.106 It would be used not only by Institutions and IRBs, but by investigators when discussing research to prospective subjects. The details need to be worked out, but something as straightforward as a checklist with the following items could focus everyone’s attention on the essentials of informed consent to any research project: (1) You are being asked to join a research project (describe it); (2) This is how it will affect your care (including that a protocol will be followed instead of your physician’s medical judgment); (3) These are the potential risks and benefits of joining the study (explain, always include any risks of death or disability); (4) You have no obligation to become a research subject, and you will be provided with routine clinical care if you decline; (5) You can change your mind at any time and leave the study; and (6) A name and phone number of someone who can answer questions.

CONCLUSION

Jay Katz, the leading authority on informed consent, always stressed the differences between research and treatment, and the desire of both the research subject and the physician-researcher to transform research into treatment for their own comfort.107 He also criticized Ed Pellegrino for asserting that “the ethical sensitivity of the investigator remains an integral part of the moral equation. . . . [because] [t]he investigator decides how much to tell the patient or family, which facts to emphasize, which to withhold, and how to present them.”108 Katz thought that Pellegrino’s view represented the old paternalism; but this was not Pellegrino’s intent. Instead, as Pellegrino himself put it in “A Response to Jay Katz,” Pellegrino had argued throughout his paper “repeatedly that it is because physicians have

106. ATUL GAWANDE, THE CHECKLIST MANIFESTO (New York, Henry Holt and Co., 2009). This idea was suggested to us by Alice Dreger of Northwestern University, who also spoke at the August 28 hearing, supra note 49.
107. See generally, JAY KATZ, EXPERIMENTATION WITH HUMAN SUBJECTS (1972).
such power to manipulate the ‘invitation’ to participate that they have an awesome moral responsibility to safeguard both autonomy and bodily integrity.”

Pellegrino underlined that his “message was simply this: the fact that physicians can manipulate consent confers not the privilege to do so but the obligation to avoid doing so.”

Katz and Pellegrino are both correct. Both agree that like all risky interventions, whether characterized as treatment or research, neonatal interventions require informed consent. Informed consent requires that the proposed procedure be explained, including how it does (or does not) differ from standard treatment and whether it poses any risks of death or disability. This seems to be a core problem in the entire discussion of the consent process in the SUPPORT study: many researchers (and IRBs) seem to believe that there is no legal requirement to obtain the patient’s informed consent to medical care (“standard of care”), and that the only relevant law for research are the federal research regulations. This view is so mistaken as a matter of law (and ethics) that we term it “legal blindness,” in that the researchers seem to be blind to both the common law and state statutes on consent to medical treatment. Why this blindness would manifest itself so strongly in the NICU is not entirely clear, but it likely has to do with the desire to deny death, or at least not to openly acknowledge it.

We think it is the centrality of death to both neonatology and neonatal research that is the elephant in the delivery room (and the NICU) here. The therapeutic illusion is also strong in this context, but in the NICU it is likely to be as strong on the physician’s part as on the patient’s part. The American characteristic of denial of death is in overdrive in the delivery room as well. The soon-to-be-mother wants the best for her baby, and the last thing she wants to know is that she might be doing something that could increase her baby’s risk of death. The neonatologist likewise wants the best for his or her newborn patients—and will do all in his or her power to deny that anything neonatology is doing could be harmful to the baby. Because both parents and physician have a strong motivation to deny death, it is, as we think Jay Katz would assert, relatively easy for them to suppress the discussion of death completely. The risk of blindness is important in SUPPORT, but less important than the risk of death. Disclosure of risks of death is always challenging, but this challenge is not met by avoidance and rationalization.

This brings us back to the deficient consent form which began the SUPPORT dispute, the failure to disclose the risk of death. The UAB

109. Pellegrino, supra note 1, at 57 (emphasis in original).
110. Id. (emphasis in original).
consent form that OHRP criticized disclosed only one risk: The “possible risk of skin breakdown at the site of [the pulse oximeter] will be minimized by your baby’s nurse moving the oximeter to another arm or leg a couple of times a day.”\textsuperscript{112} This reflects a central point both Jay Katz and his star student/colleague Alexander Capron have made. In a 2006 tribute to Jay Katz, Professor Capron wrote that “even when investigators acknowledge an obligation to obtain subjects’ informed consent, their aversion to confronting what is really at issue can produce some very striking displacement.”\textsuperscript{113} Capron recalls an example provided by Katz who had criticized a UCLA research project on schizophrenic patients whose medication was withdrawn to study whether it was possible to predict a relapse. Katz recognized the importance of the study, but was critical of the investigator’s inability to distinguish treatment from research, and refusal to warn the subject of the dangers of relapse. Instead, as Professor Capron described it, “the consent form ironically went into exquisite detail about the trivial risks of a needle prick to obtain blood sample.”\textsuperscript{114} This disclosure could have lulled subjects into thinking, as Katz had suggested, “that the investigators would disclose any other risks in similar detail and with similar candor.”\textsuperscript{115} Capron continues with his own observation, “Having read hundreds of consent forms over the years [he is] convinced that investigators often unconsciously displace their anxiety over truly worrisome points by paying attention to minor risks about which they can offer more reassurance.” Capron concludes: “Unfortunately, this practice implicitly makes the process of prior IRB review and subject consent seem like much ado about nothing.”\textsuperscript{116}

Capron could be describing the concentration on the risks of a skin rash (rather than the risk of death) in the SUPPORT study. Later he goes on to suggest that in cancer trials at least, physician-researchers may be taking advantage of the “therapeutic illusion” cancer patients have that the trial may benefit them. In the SUPPORT study it seems reasonable to conclude that the researchers were not trying to exploit their subjects; rather that they were in a mutual conspiracy with them to imagine that no real research was being conducted, only “standard of care” treatment. This is a mutual self-

\textsuperscript{112} UAB CONSENT FORM, supra note 10, at 4.
\textsuperscript{113} Id. at 3-4; Alexander M. Capron, Experimentation with Human Beings: Light or Only Shadows? 6 YA L J. HEALTH POL’Y L. & ETHICS 431, 441 (2006). Another speaker at the August 28 meeting was Dr. John Lantos, who suggested that prospective research subjects be told that the research outcomes could actually turn out to be better than standard care. This is true, but concentrating on this hope is just another way to avoid confronting the risk of death. John D. Lantos, The Weird Divergence of Ethics and Regulation With Regard to Informed Consent, 13 AM. J. BIOETHICS 31, 32 (2013).
\textsuperscript{114} Capron, supra note 113, at 441.
\textsuperscript{115} Id. (citing Jay Katz, Human Experimentation, supra note 2, at 47).
\textsuperscript{116} Capron, supra note 113, at 442.
deception that both parents and physician are more than willing to engage it; the parents because they don’t want to acknowledge that anything worse than a skin rash could happen to their baby; the physician because he or she doesn’t want to acknowledge that the research project could be putting half of the randomized extremely premature infants at a higher risk of death. The researchers can thus be described as being blinded in two ways: first by imagining that the study was not research at all, but simply treatment (the application of “standard of care” medicine), and second, by convincing themselves that the law of informed consent does not apply to treatment. The radically paternalistic result would be that physicians could not only set the “standard of care” for medical interventions—whether research or treatment—but also set the “standard of care” for informed consent for both. That quest is, we think, dangerous to the autonomy and dignity of patients and should be repulsed not only by patients, research subjects, and the public, but by physicians and researchers as well.