JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 9, No. 8, August 2013 "Happy Trials to You"

What is a "Reasonably Foreseeable Risk"? The SUPPORT Study Controversy

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Abstract

On March 7, 2013, the Office of Human Research Protections (OHRP) sent a determination letter to the University of Alabama at Birmingham (UAB) stating that the neonatology study titled, "Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)" did not comply with regulatory requirements to provide parents with a description of the reasonably foreseeable risks of the study because the consent form did not contain information about the risks of being randomized to one of two different groups (lower vs. higher blood oxygen saturation). Several commentators strongly disagreed with OHRP's determination. In response, OHRP sent UAB another letter on June 4, 2013, acknowledging that there is widespread misunderstanding about the disclosure of research risks in clinical trials similar to the SUPPORT study, and put its administrative actions on hold, pending issuance of further guidance. This article argues that opposing opinions concerning the adequacy of informed consent in the SUPPORT study resulted from different interpretations of what constitutes disclosing reasonably foreseeable risks to research subjects. To help clarify these issues, federal agencies should publish guidance on what is meant by "reasonably foreseeable risks."

Introduction

On March 7, 2013, the Office of Human Research Protections (OHRP) sent a determination letter to the University of Alabama at Birmingham (UAB) concerning allegations of non-compliance in a study titled, "Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)." This neonatology study was funded by the Department of Health and Human Services (DHHS) through the National Institutes of Health (NIH)[1]. OHRP determined that the study did not comply with DHHS' regulatory requirement to provide parents with an adequate description of the reasonably foreseeable risks of the study because the consent form did not contain information about risks related to being randomized to one of two different groups (lower vs. higher blood oxygen saturation). OHRP required UAB to submit a plan to ensure that all subsequent consent documents approved by its institutional review board (IRB) will comply with DHHS consent requirements[1]. After learning about OHRP's finding, the consumer advocacy group Public Citizen called on DHHS to apologize to the parents of the neonates and launch an independent investigation of ethical problems with the study[2]. Various commentators, including representatives from the NIH, SUPPORT investigators, the editor of the New England Journal of Medicine (which published the study results), pediatricians and bioethicists disagreed vociferously with OHRP's determination[3-8]. In response, OHRP sent UAB another letter on June 4, 2013 acknowledging that there is widespread misunderstanding about the disclosure of research risks in clinical trials similar to the SUPPORT study, and put its administrative actions on hold, pending issuance of further guidance[9].

When competent scientists and scholars have polarized opinions concerning a clinical study's compliance with ethical and legal requirements, it is likely that they are disagreeing about more than just the facts concerning the research. This article will argue that opposing viewpoints concerning the adequacy of the informed consent document used in the

SUPPORT study resulted from different interpretations of what constitutes disclosing reasonably foreseeable risks to research subjects or their representatives.

The SUPPORT Study

Research sites in the National Institute of Child Health and Human Development (NICHD)'s Neonatal Research Network conducted the SUPPORT study. SUPPORT had two aims: (1) to learn more about the benefits and risks of using continuous airway pressure (CAP) to help the lungs of neonates in the intensive care unit (ICU) remain inflated; and (2) to determine the optimal level of blood oxygen saturation for neonates receiving CAP[10]. The study enrolled 1,316 infants born between 24 and 28 weeks gestation at 22 research sites. RTI International, a contract research organization, served as an independent data coordinating center for the study. UAB was the lead site for the second aim of SUPPORT. IRBs at each site and RTI approved the study[11].

Pediatricians started giving supplemental oxygen to premature infants in the 1940s to increase lung function and reduce the risk of death and brain damage. Research conducted in the 1950s showed, however, that giving neonates too much oxygen was associated with a number of health problems, including retinopathy of prematurity (ROP), a condition involving disorganized growth of retinal blood vessels that can lead to impaired vision and blindness[11]. In response to these findings, pediatricians started giving less oxygen to premature infants, but research conducted in the 1970s showed that giving premature infants some, but not enough, oxygen increases the risk of death, so pediatricians revised their practices once again and began giving more oxygen[11]. At the initiation of the SUPPORT study, the standard of care for premature neonates receiving CAP was to maintain blood oxygen saturation between 85% and 95%[1].

The SUPPORT study sought to determine the oxygen saturation level that best minimizes the risks of ROP and death. To achieve this goal, the study randomly assigned neonates to a group receiving 85%-89% oxygenation or one receiving 91%-95%. The investigators used pulse oximeters to monitor oxygen levels. The study took place from February 2005 to February 2009. The results were published in 2010[10]. Between January 2003 and December 2007, the Neonatal Research Network collected data on 9,575 infants born between 22 and 28 weeks gestation, including 8,259 who were not in the SUPPORT study[11].

The SUPPORT study found that the lower oxygenation group had a significantly lower risk of ROP, as compared to the higher oxygenation group (8.6% vs. 17.9%), but also a higher risk of death before discharge from the ICU (19.9% vs. 16.2%)[10]. Infants in both groups had a lower mortality rate than those in the control group[10,12]. By obtaining a more precise estimate of the optimal oxygenation level for premature infants, the SUPPORT study provided valuable information for clinicians, which is likely to have a positive effect on medical practice. In response to the study, the American Academy of Pediatrics revised its recommendations for oxygen saturation in premature infants[7], which may lead to a change in the standard of care.

OHRP's Critique of the Consent Form

All of the institutions participating in SUPPORT used a common consent form template, with various minor modifications made by different institutions. Because UAB was the lead institution for the randomization involved in the study, OHRP's determination letter focused on UAB's consent form. However, the agency also found similar problems with the consent forms used by all of the institutions[1]. OHRP's main allegation against UAB was that the consent form did not adequately inform parents about the risks of the study[1]. The applicable DHHS regulation (also known as the Common Rule) requires that informed consent provides

a "description of any reasonably foreseeable risks or discomforts to the subject"[13]. The language in UAB's 2004 version of the consent form described the risks of the study as follows:

> The possible risks of using CPAP/PEEP include stomach bloating and a temporary slowing of the heart rate. Another possible risk is collapsing one of both of the lungs. Use of the CPAP/PEEP at the level used in this study does not increase the risk of collapsed lungs. Like with the use of CPAP/PEEP, a possible risk of being intubated (placed on the breathing machine) may include a temporary slowing of the heart rate or possibly the collapse of one or both lungs. Another risk is the possibility of the airway being punctured. Other possible risks include bruising or cutting of the tongue, gums or airway. Other potential risks during resuscitation after birth include the need for chest compressions, rescue medications, and even death. It is not thought that the use of either of these ways of delivering oxygen increase risks. Pulse oximeters are used routinely in thousands of premature infants in the United States every day. 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 [14, pp. 3-4].

The protocol was later amended to include a sub-study of neurodevelopment, using magnetic resonance imaging (MRI), and a sub-study of infant growth. The amended consent form discussed risks associated with the MRI and growth measurements, but did not include any additional discussion of the risks of randomization[15].

OHRP contended that this description was inadequate because it did not include risks associated with randomization to one of the two groups (lower vs. higher oxygen saturation levels). The consent form did describe the aims of the study in general terms and random assignment to the two groups. It also informed the parents that the normal range of oxygen saturation for premature infants was 85% to 95%, and that doctors will adjust oxygen levels up or down if the infant's oxygen saturation falls below or exceeds these levels[11]. OHRP claimed that random assignment to the lower or higher oxygen group might increase the risk of death or ROP, respectively, because there was evidence that levels of oxygen below 85% increase the risk of death and that levels above 95% increase the risk of ROP: "The researchers had sufficient available information to know, before conducting the study, that participation might lead to differences in whether an infant survived, or developed blindness, in comparison to what might have happened to a child had that child not been enrolled in the study."[1, p.7]

According to OHRP, parents should have been informed about these risks:

> It would have been appropriate for the consent form to explain (i) that the study involves substantial risks, and that there is significant evidence from past research indicating that the level of oxygen provided to an infant can have an important effect on many outcomes, including whether the infant becomes blind, develops serious brain injury, and even possibly whether the infant dies; (ii) that by participating in this study, the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received, though it is not possible to predict what that change will be; (iii) that some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind; and (iv) that the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death[1, p.10].

The essence of OHRP's determination was that the researchers should have informed the parents of the risks of the two treatment groups, even though both treatments were within standard of care.

Responses to OHRP

Many different commentators took issue with OHRP's determination letter. All of these commentators argued that there was a lack of evidence of increased risk related to random assignment to one of the two treatment arms, so there was no need to inform participants about these risks[4-8].

David Magnus and Art Caplan[4] argued there was no evidence of increased risk because the infants would have oxygen saturation maintained within the standard of care (85% to 95%). Since there was variation in actual practice within the standard-of-care range, infants who participated in the study would have the same chance of receiving higher or lower oxygen levels within this range as those who were not participating in the study, according to Magnus and Caplan:

> Given that there was variation in clinical practice at the time the study was mounted, it is not clear how randomization among treatment options could have created novel risk over random physician preference… There were and continue to be well-understood risks in following accepted treatment options involving oxygen administration to extremely underweight babies — but there was no evidence that randomization to one option or another increased that risk[4, p. 1865].

There was no need to inform parents about the risk of randomization, according to Magnus and Caplan, because there was no evidence that randomization increased the risk of ROP or death[4].

New England Journal of Medicine editor Jeffrey Drazen and colleagues pointed out that the clinical trial was conducted, in large part, to try to clarify the risks associated with different levels of oxygen saturation. It was only after the trial was completed that one could say, with the benefit of hindsight, that infants in the lower oxygen group had a greater risk of death than those in the higher oxygen group, while those in the higher oxygen group had a greater risk of ROP. Since investigators did not know this at the outset of the trial, they should not have been expected to communicate this risk to the parents[3].

John Lantos[6] also maintained that there was no evidence that random assignment to the different treatment groups placed infants in the SUPPORT study at a greater risk of ROP or death, compared to infants not in the study. Lantos also noted that the evidence has shown that the infants in both arms of SUPPORT had a lower rate of death than the control group of infants in the Neonatal Research Network. He agreed with Magnus and Caplan and other commentators that there was no need to inform parents about the risks of random assignment to two different groups, since there was no evidence that there would be any additional risk from this study design, but he conceded that the parents should have been better informed about the goals of the study[6].

Kathy Hudson, Alan Guttmacher, and Francis Collins, representatives from the NIH, published a commentary that offered a slightly more conciliatory response. They argued that the SUPPORT investigators had no reason to expect that random assignment to one of the two groups would increase the risk of death or retinopathy, based on the available data. They expressed strong support for OHRP's role in overseeing research involving human participants and acknowledged that its determination letter provides the clinical research community with an opportunity to have an informed dialogue about what constitutes a reasonably foreseeable risk within the context of comparing two treatments considered to fall within the standard of care[7].

A letter to the editor of the New England Journal of Medicine, signed by 26 physicians and bioethicists, opined that the evidence did not support OHRP's view that the different groups in the SUPPORT study faced increased risks due to differing oxygen saturation levels[8]. The letter stated that OHRP's claim that the SUPPORT investigators did not adequately inform parents of reasonably foreseeable risks was a "substantive error and will have adverse implications for future research."[8, p.e36]

OHRP Responds to the Critics

In response to these and other critics, OHRP sent UAB another letter on June 4, 2013. OHRP emphasized that it did not question whether the design of the study was ethical; it only took issue with the informed consent related to the study. OHRP reiterated its contention that the consent document did not adequately inform parents about reasonably foreseeable risks because it did not tell them about the increased risk of death from lower oxygen levels or the increased risk of ROP from higher ones. OHRP tried to rebut the argument that there were no increased risks to the participants because their oxygen saturation levels would still fall within the standard of care:

> [F]or at least some of the children participating in the SUPPORT trial, the effect of such participation was to specifically increase their likelihood of being assigned to oxygen levels close to either end of the range of standard care — and thus to oxygen levels at which, as a clinical matter, they would not have been assigned by their individual physicians, had they not been in the study… For some if not many of the subjects in the SUPPORT study, research participation increased the chance that they were treated at one or another end of the standard of care range. Given the requirement that subjects be apprised of "reasonably foreseeable risks," it would seem appropriate that the parents of the infants should have been informed of the real concerns within the medical community regarding those oxygen levels[9, p. 4].

OHRP conceded that there was considerable controversy about the disclosure of risks related to the SUPPORT study and acknowledged that it has an obligation to provide clear guidance to the research community. To meet this obligation, the agency stated that it was planning to develop additional guidance, following a public meeting and solicitation of input from interested parties. Its administrative actions against UAB would be put on hold, pending issuance of the new guidance[9].

Which Risks Should be Disclosed?

OHRP and its critics had access to the same facts and the expertise to assess them, but presented different arguments. When competent, well-informed parties disagree about the ethical and legal aspects of a study, it is likely that they are disagreeing about more than the facts. In this case, the disagreement was about communicating reasonably foreseeable risks to the subjects (or their representatives). As mentioned above, OHRP acknowledged, in its June 4 letter, that there was widespread disagreement concerning these issues. The commentary from NIH officials also stated that the dispute was about how to interpret the regulations: "We respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPORT study commenced."[7, p. 2350]

The source of the disagreement between OHRP and its critics was the phrase "reasonably foreseeable risks," which the federal regulations do not define[13]. Since the regulations do not define "reasonably foreseeable risks," investigators, IRBs and oversight agencies might each interpret this phrase differently. These different interpretations can lead to confusion and controversy, as appears to have happened here. Inconsistent interpretations, by

definition, lead to inconsistent protection of human research subjects, which can lead to inadequate protections in some instances.

To shed light on the SUPPORT dispute, it is useful to consider how one might interpret the phrase "reasonably foreseeable risks." The phrase comes directly from tort law. In tort law, a reasonably foreseeable risk is a potential harm that a reasonable person would be able to anticipate or predict as a result of his or her actions[17]. For example, a reasonable person who mops the floor in a grocery store should be able to anticipate that someone could slip and fall on the wet floor. To help avert this harm, a reasonable person would put up a warning sign on the floor[17]. This definition is not very useful, however, because "reasonable person" must also be defined, and there are different explanations of this phrase in legal decisions and jurisprudence[17]. Sometimes the reasonable person is understood as the average person, but more often, the reasonable person is understood normatively, i.e., the reasonable person does what one *should* do in a particular situation, not what the average person *actually* does in that situation. For example, the average person *actually* breaks the speed limit when driving on a regular basis, but that does not mean the reasonable person *should* break the speed limit. Thus, tort law's reasonable person doctrine still does not get us very far, since it does not help us determine what the average person should do. Moreover, in the research context, we need to focus on what the average *researcher* should do, not on what the average *person* should do, since researchers have specialized knowledge that they should employ to inform subjects about risks.

Since the law does not shed much light on how to interpret the phrase "reasonably foreseeable risks," perhaps we should look to other sources of insight, such as philosophical analysis, which involves the careful examination of the meanings of words and concepts[18]. The words that require additional clarification are: "reasonable," "foreseeable" and "risk."

Let's consider the term "foreseeable." Something is foreseeable if it can be predicted or anticipated. What makes prediction reasonable? To be reasonable means to follow accepted standards for forming beliefs and opinions and making decisions. One could argue that prediction is reasonable when it is based on evidence from empirical research, past experience, or general scientific principles, as opposed to speculation, a gut feeling, or superstition. Predicting the winner of an election based on reading tea leaves would not be reasonable, whereas predicting the winner based on well-designed opinion polls would be. Putting these two ideas together, we can say that a risk is reasonably foreseeable when it can be predicted on the basis of evidence.

A risk is an exposure to a chance of a harm or loss. When we say that a fireman risked his life saving a child from a fire, we mean that he exposed himself to the chance of injury or death. The notion of "chance" may be interpreted differently, depending on the type of evidence we have for a risk. If we have enough evidence concerning a risk that we can assign a probability between 0 and 1 to its occurrence, we can call it a "probabilistic risk." For example, suppose you are deciding whether to play Russian roulette and you know there is only one bullet in a pistol with six chambers. You have a one in six chance (or 0.167 probability) of shooting yourself in the head. Or suppose you are an otherwise healthy person who needs to undergo general anesthesia for an appendectomy. Your anesthesiologist could estimate that you have about a four-in-one-million chance (or 0.000004 probability) of dying as a result of the anesthesia, based on empirical evidence[19].

If we do not have enough evidence to assign a probability between 0 and 1 to a risk, but we have some evidence to believe that the risk might materialize, we can call it a "possible risk." For example, suppose you are considering playing Russian roulette and you do not know whether there are any bullets in the gun. We would say that it is possible that you could shoot yourself in the head, even though we can't assign a probability to this event. Even if we cannot assign a probability to the occurrence of a possible risk, we may still be

able to say whether it "likely," "unlikely," "highly unlikely," etc. For example, getting attacked by a tiger is a possible risk of visiting the zoo, since we have evidence that this unfortunate event can happen but not enough evidence to estimate the probability that it will occur. Most people would say that getting attacked by a tiger while visiting the zoo is a highly unlikely event, even if they cannot estimate the probability that this event will occur.

We sometimes speak of "known risks" vs. "unknown risks." Known risks are risks for which we have enough evidence to predict likelihood. These risks may be probabilistic or possible risks, depending on the type of evidence we have. For example, getting attacked by a tiger is a known, though highly unlikely, risk of visiting the zoo. An unknown risk is one we have almost no evidence for, so, by definition, we cannot reasonably predict or anticipate it. In dealing with the threat of terrorism, for example, there may be many threats that we cannot anticipate at this time. However, the government may acquire enough information about terrorist activities to convert certain types of terrorist threats into known risks. An important part of risk management, whether in business, law or medicine, is to increase our knowledge of risks, so that we can prepare for them[16].

Finally, we also need to consider the "severity" (or magnitude) of a risk[16]. Severity is a function of the harms or losses associated with a risk. A "severe risk" is associated with catastrophic harms, such as death, disability or hospitalization; a "moderate risk" is associated with less severe harms, such as an unpleasant allergic reaction, fever, fatigue or nausea; a "minimal risk" is associated with minor harms, such as limited bleeding or bruising, or temporary, tolerable pain. Federal research regulations define minimal risks as those in which "the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests"[20]. Severity is an important factor to consider when informing individuals about risks. Most people would want to know whether a medical procedure involves a risk of death, even if the chance of dying is very small. For example, although the probability of death from general anesthesia is very small, physicians should inform their patients about this risk because the outcome is catastrophic.

A person making an important decision would want to know about reasonably foreseeable risks, both known and possible. Indeed, it is standard practice in medical informed consent to inform patients about the reasonably foreseeable risks, both known and possible, of different treatments and procedures[21]. For example, when informing a patient about the risks associated with statin drugs used to lower blood cholesterol levels, a doctor might inform the patient that these drugs have a number of risks (or side effects), such as muscle weakness, memory loss, liver damage, and diabetes. The label on the medication will also list various risks[22]. Some of these risks will have a known probability of occurring, while others will not. In either case, it would be ethical (and legally advisable) to inform the patient about both types of risks, since this information could be relevant to their decision to take the drug[22].

Clinical investigators also disclose known and possible risks when obtaining informed consent for research participation[21]. For example, suppose a study is collecting medical histories and blood and cheek scrapings for research on the genetics of diabetes. The investigators should inform the subjects that the risks of a blood draw include bleeding, bruising or infection at the site. These would be known risks because investigators can estimate the probability that they will occur, based on past experience or other evidence. Since they are collecting genetic and health information, they should inform participants that inadvertent release of this information could lead to discrimination in employment or insurance[23]. These would be possible risks because investigators have reason to believe that discrimination could happen as a result of inadvertent release of information, but they do not have enough evidence to estimate the probability of its occurrence. Although this risk is

merely possible, one could argue that investigators should disclose it because it is a real risk that is likely to concern research subjects[24].

Disclosing the Risks of Randomization in the SUPPORT Study

The text from OHRP's letters and the commentary from its critics indicate that there may have been a disagreement about the types of risks that should be disclosed to participants. The text from OHRP's March 7 determination letter indicates that the agency was concerned about the disclosure of possible risks related to randomization to the two treatment groups. The letter states that the informed consent form "does not say that there *may* be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group" and "does not say that being in the upper range group *may* result in a greater risk of developing ROP[1, pp. 8-9, emphasis added]." The letter also says the investigators had "sufficient available information to know, before conducting the study, that participation *might* lead to differences in whether an infant survived, or developed blindness, in comparison to what *might* have happened to a child had that child not been enrolled in the study[1, p. 7, emphasis added]." In its June 4 letter, OHRP referred to "potential" risks several times[9]. By using the words "may, "might" and "potential," OHRP was implying that these risks are possible ones. To indicate that the risks were probabilistic, OHRP could have used more definite phraseology.

OHRP's critics all focused on the lack of evidence for increased risks due to random assignment to the different oxygen saturation groups. Magnus, Caplan and Lantos said there was no evidence for increased risks; the group of 26 physicians and bioethicists said the evidence did not support the view that there were increased risks; and the NIH representatives said that there was no reason to expect any increased risk. While it is clear that OHRP's critics did not believe that there was enough evidence to claim that random assignment to different treatment groups created *probabilistic* risks, it is not clear whether any of the critics believed that there was sufficient evidence to that claim random assignment created *possible* risks. Indeed, most of OHRP's critics did not directly address the issue of whether random assignment to different treatment groups created possible risks. Only Lantos addresses questions of possible risks: "[OHRP's] position is apparently that informed consent forms need to inform parents not only of known risks and of possible risks, but also of risks that the investigators did not think were possible — even after those risks have been shown not to exist[6]." While Lantos seems to think that random assignment to different treatment groups did not even create possible risks, it is not clear whether the other commentators held the same view.

Regardless of what the commentators had to say, were there good reasons to believe that random assignment of infants to different treatment groups in the SUPPORT study created possible risks? As the commentators point out, the infants in the SUPPORT study would be treated within the standard-of-care range (85%-95% oxygen saturation), so there was no reason to believe at the outset of the study that *aggregate* risks to infants in the study would be higher than those not in the study (who, presumably, received the standard of care). However, since the infants in the study were divided into lower and higher oxygen saturation groups, infants in those groups could have faced higher risks of death or ROP than infants not in the study, who might, for example, have received oxygen saturation in the middle of the standard-of-care range.

Study subjects may have also incurred additional or different risks compared to the standard of care for a specific institution or physician. For example, a physician/investigator might typically treat his or her clinical patients at the low end of the range, shifting the risk profile toward death and away from ROP. The study might also have increased (or decreased) subject risk by limiting the flexibility of physician/investigators to adjust

oxygenation level across the entire 85% to 95% range or beyond. It is reasonable to suppose that the available information at the beginning of the study backs OHRP's view that randomization increased the possible risks of death for the lower oxygen saturation group and ROP for the higher one, compared to care that would have been received outside the study. Furthermore, the study did not allow parents to express their risk preferences for death vs. ROP, albeit an unappealing choice.

The researchers did not know how these risks would play out — that's what the study sought to determine — but they did know that higher oxygen saturation (in general) was associated with ROP and lower saturation (in general) was associated with death, and they sought to ascertain the ideal level of saturation that best minimized both of these risks. Although it turned out that the infants in the SUPPORT study did better than those who were not in the study, this fortunate outcome is irrelevant to the consent issues, which should focus on the available information at the outset of the study.

Of course, the fact that randomization created possible (or even probabilistic) risks does not mean that the investigators should have informed the parents about them. The OHRP critics who downplayed the risks could have admitted that randomizing infants to different treatment groups created differential risks, but maintain that there was no need to inform the parents about them, because the risks were highly unlikely. This would have been a reasonable point. Perhaps the parents did not need to know about these risks. Perhaps worrying about these risks would have distracted the parents from considering more important risks and benefits of the study and actually undermined the consent process by focusing their attention on minor considerations. However, making this point is not the same as claiming that these risks did not exist, as some OHRP critics have suggested. Moreover, the critics never made the argument that the investigators should not inform the parents about risks that are highly improbable or unlikely.

Implications

This dispute about risk communication has implications for clinical research that reach beyond the SUPPORT study[3,4]. Comparative effectiveness research (CER), such as the SUPPORT study, is designed to inform medical decisions by providing clinicians and patients with information concerning the safety and efficacy of different treatment options[25]. Investigators may analyze pre-existing evidence, observe future clinical evidence, or conduct randomized controlled trials (RCTs) to generate new evidence.

In superiority trials involving accepted treatments, the goal is determine whether one is better than the others in terms of safety and/or efficacy[26]. All of the treatments fall within the standard of care, and the scientific evidence does not indicate whether one is superior to the other at the outset of the study, i.e., the treatments can be said to be in clinical equipoise. (However, it may be known prior to a study that different study treatments have different risk/benefit profiles.) Subjects are randomized to different groups in order to minimize bias. In these studies, randomization itself is not supposed to create known risks, because the evidence does not indicate whether one treatment is superior to the other.

Nevertheless, randomization might create possible risks if the different treatments have different risk profiles, and, following OHRP's logic, participants might need to be informed about these risks. If one holds that the parents of the infants enrolled in the SUPPORT study should have been informed about the risks related to random assignment to different oxygen saturation levels, it follows that participants in many other superiority studies should be informed about the possible risks of randomization, provided the different treatments have different risk profiles. Adopting this rationale could require investigators to rethink the consent process in superiority trials and other RCTs involving the comparison of two or more

treatments. It might also deter patients who are concerned about these possible risks from participating in these studies, which would adversely impact CER.

Conclusion: Additional Guidance Needed

The current controversy is an opportunity to address important issues in human subject protection. Should the investigators have informed parents of the possible risks of random assignment in the SUPPORT study? OHRP said "yes," but many commentators and 23 IRBs said "no." If one assumes that the parties on opposite sides of this issue have a reasonable understanding of the scientific, medical, ethical and legal aspects of the research, it is likely that the dispute involves a conceptual disagreement, not just a factual one. The texts from OHRP's letters and the responses from critics suggest that a key point of contention is interpretation of the phrase "reasonably foreseeable risks." Since federal research regulations do not define this phrase, it should come as no surprise that different investigators and IRBs can interpret it differently. To help clarify these issues, OHRP has indicated that it will issue guidance for investigators and IRBs concerning the disclosure of "reasonably foreseeable risks." This is a welcome development. Other agencies, such as the Food and Drug Administration, should also issue guidance and provide illustrative examples. The guidance should also create a risk nomenclature and address questions about whether risks are known, possible, probable, likely, severe, moderate and so on.

Investigators who conduct studies (and the IRBs that review them) that randomize subjects to different treatment groups that fall within the standard of care should consider more carefully whether their research nevertheless creates risks that require disclosure, e.g., potential harms due to different risk profiles associated with different treatment groups.

Acknowledgments

This article is the work product of an employee or group of employees of the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH). However, the statements, opinions or conclusions contained therein do not necessarily represent the statements, opinions or conclusions of NIEHS, NIH or the United States government.

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