Informed Consent for Comparative Effectiveness Research Should Include Risks of Standard Care

Lois Shepherd

Recent research controversies and debate have called into question whether existing ethical norms and regulatory structures adequately address the challenges of comparative effectiveness research (CER). CER studies "compare outcomes between patients who receive... different treatments that are... in widespread use."[1] The "core question of CER" is "which standard interventions work best for whom."[2] Examples include studies that randomize subjects to two hypertension drugs in widespread use,[3] or varying amounts of radiation for cancer treatment, with trade-offs between toxicity and control,[4] or surgery versus medication when either is considered acceptable.[5] Other names for CER are "pragmatic trials," "research on medical practices,"[6] and "standard of care studies."[7]

Much of the debate about CER has been over consent — the kind of disclosures necessary for the consent of research subjects to be considered properly *informed*, but even whether obtaining consent is or should be required. This debate takes place within a larger conversation about whether certain traditional precepts of research ethics remain valid, such as the requirement that research participation be voluntary[8] or that clinical care and research be understood as fundamentally distinct.[9] A number of prominent scholars are calling for changing the regulatory requirements for oversight, voluntariness, and disclosures to subjects in order to facilitate "learning health care systems."[10] For some who advocate change, the current oversight system, borne of scandal, is outdated, and a new paradigm is in order.[11] Research subjects are overprotected, they argue, and patients underprotected when onerous regulatory requirements thwart the research needed to determine what works for patients and what doesn't.[12] Others believe that the traditional requirements of voluntariness and consent remain valid — no bold new paradigm is in order — but nevertheless argue that these requirements have been recently misinterpreted or misapplied to CER studies in a heavy-handed, research-stifling manner by the federal agency charged with research oversight, the Office for Human Research Protections (OHRP).[13]

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In general, advocates for changing the way CER is regulated — whether calling for fundamental change to current research ethics norms or merely exceptions in their application to CER — see research that compares variations in clinical practice as fundamentally distinct from research involving experimental, unproven, or unapproved therapies.[14]

This article argues the opposite. The promise of comparative effectiveness research does not justify abandoning the fundamental principle of voluntariness or for discounting the fact that clinical care and research are pursued for different aims even as they become more frequently combined.[15] CER does not require a new paradigm for informed consent, or even new regulatory requirements for the disclosure of risk. OHRP has been right on this score. While not perfect, the regulations for the protection of human subjects match well the ethical principles set out in the Nuremberg Code and the Belmont Report, which — whether borne of scandal or not — remain compelling.

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The crux of the argument of those who want diminished consent requirements for randomized CER is that patients are receiving care they might have received outside a research study and therefore the risks to which they are exposed are risks of clinical care and not of research. But in randomized CER, patients' care may be altered in order to study the risks and benefits of various treatments. Whether any individual patient's care is altered depends on the lottery of randomization, but by participating in such a study, the patient — now a *patient-subject* — is exposed to an altered course of care and its potential associated risks and benefits. Because their care, and the risks to which they are thereby exposed, are altered for research purposes — that is, to gain knowledge for the purpose of helping future patients — these patient-subjects are entitled to receive information about those risks just as they would if volunteering to participate in research on experimental interventions. Otherwise, their consent is not informed, and their participation in research is not voluntary. They start to resemble other populations who have been exploited in the past because their location (the clinic or hospital) and vulnerability (their need for medical care) make them convenient for researchers.

Informed consent for randomized CER should, *must,* include risks of standard care. This article explains why, in a randomized CER study, risks from standard care treatments are "risks of research" and not just risks of clinical care, and, if those risks are more than minimal, they must be disclosed. After briefly reviewing historical and present ethical, legal, and regulatory norms of consent, the article uses the SUPPORT Study controversy to explain how and why these disclosures are legally and ethically required.

Ethical, Legal, and Regulatory Norms of Consent

The Nuremberg Code begins, "The voluntary consent of the human subject is absolutely essential. This means that the person involved should…have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision."[16] The Belmont Report, setting out three basic ethical principles — respect for persons, beneficence, and justice — states that "[r]espect for persons requires that subjects…be given the opportunity to choose what shall or shall not happen to them."[17] Such respect is lacking when information has been withheld that pre-

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vents potential subjects from making a "considered judgment."[18] The Report further acknowledges that because participation in research is voluntary, the research subject "may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care."[19]

In addition to these well-established ethical norms, there are also legal duties to obtain informed consent before altering patients' care for research purposes.[20] The common law protects an individual's right to make decisions affecting his or her body.[21] When treatment decisions are made for considerations other than the patient's preferences and medical best interests (e.g., for research purposes), those reasons must be disclosed.[22] If state action is involved, constitutional rights may also be implicated.[23] Although there are few reported research injury cases, those precedents that do exist indicate that "[a] human subject is entitled to *all* material information,"[24] meaning information material to a decision to participate in research. Maryland's highest court in *Grimes v. Kennedy Krieger Institute, Inc*., made a special point of stating that "[t]he fact that if [certain] information was furnished, it might be difficult to obtain human subjects for the research, does not affect the need to supply the information, or alter the ethics of failing to provide such information."[25]

The Common Rule, which sets out human subjects protections for federally funded research in the United States, provides more specific guidance about what must be disclosed,[26] as do the regulations of the Food and Drug Administration.[27] Requirements for informed consent include, among other things, an explanation of the purposes of the research and a description of "any reasonably foreseeable risks or discomforts to the subject."[28]

The question this article addresses is this: Are the risks of the different treatments being compared in CER risks that must be disclosed? While on its face the question seems easily answered — care posing nonminimal risks is altered for research purposes, yes, of course, those risks must be disclosed — the amount of debate and disagreement this question has engendered makes it important to walk through exactly why this is so.

This article breaks down the larger question — must risks of standard care be disclosed in CER? — into two separate questions in order to address the arguments made by advocates of reduced disclosures. Those advocates' arguments are generally based on the *similarity* of the research interventions to clinical care and the *uncertainty* about which is best. Therefore this article focuses on the following two questions:

1. In randomized CER studies, are risks from standard care treatments "risks of research" or are they just risks of clinical care? and
2. If the relative risk/benefit profiles of the treatments to which subjects are assigned in a CER study are uncertain — if clinicians don't know which is "better" — can the research be described as having *no or minimal risk*?

To explore these questions, it is useful to turn to the SUPPORT Study controversy, which placed these questions front and center before the research community.

The SUPPORT Study Controversy

The SUPPORT Study (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), which took place from 2005 to 2009, randomized aspects of breathing support for extremely fragile newborns, but provided parents only minimal disclosures of the attendant risks of eye disease, neurological injury, and death. When the study's results were published, revealing higher than expected infant mortality rates associated with some of the interventions, questions about the adequacy of disclosures made to parents were raised. Regulatory bodies, researchers, and research ethics scholars have since been engaged in protracted debate over the question of required disclosures in this and other studies that purport to compare existing treatments. With respect to SUPPORT, these communities were publicly and vigorously divided as perhaps over no other past research study.

To be clear, although SUPPORT is often referred to as a CER study[29] — and even by some as a "paradigm" CER study — it was not one, and understanding that it was not actually a CER study is important for identifying some of the research ethics landmines that lie beneath proposals to eliminate or reduce disclosures for CER studies. This will be explained below. First, however, a description of the study and the debate which followed it is in order. Studying SUPPORT through the lens of CER not only tracks the historical evolution of the debate over CER, but also reveals the extent to which some in the research community are willing to embrace reduced requirements for informed consent. Defending the investigators' decision to omit disclosures of all clinical risks in a study comparing treatments that can affect rates of blindness and death, reveals a readiness to omit disclosures of risks, or even omit consent altogether, in a vast array of human subject experiments.

Purpose and Design

SUPPORT enrolled over 1300 extremely premature infants in a complex study sponsored by the National

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Institute of Child Health and Human Development of the NIH.[30] It was a multi-center study involving 23 NICUs in academic medical centers. The study involved two different randomizations: In the first, premature newborns were randomized to two different methods of breathing support (continuous positive airway pressure (CPAP) vs. ventilation and surfactant use); and in the second, newborns were randomized between different levels of oxygen saturation. The purpose of the second randomization was to determine the best level of oxygen in order to reduce the risk of retinopathy of prematurity (ROP) (risk of eye disease that may result in blindness) without unduly increasing other risks of mortality or neurological harm. The published guidelines for clinical practice at the time specified an optimal range of 85% to 95% oxygen saturation, but, investigators asked, could a more precise range prove superior in terms of patient outcomes? To answer this question, infants were assigned either to a "low oxygen group," with a target saturation range between 85% and 89%, or a "high oxygen group," with a target saturation range between 91% and 95%.

The study design included intentionally altered oximeters to measure the level of oxygen in the blood of the infants, with the purpose of blinding care providers to the true level of oxygen saturation.[31] A particular infant's oximeter would reveal an oxygen saturation level of 88 to 92% as long as the infant's oxygen level was within the range to which it had been assigned (i.e., +3 percentage points for the low range and -3 percentage points for the high range). Targeting this narrower mid-range (88-92%) was, according to the consent form used at Duke University, "the aim in many units" in care provided outside the study.[32]

Results

In 2010, the investigators published the results of the study.[33] They concluded that more babies died in the low oxygen group than in the high oxygen group. "Death before discharge occurred in 130 of 654 infants in the lower-oxygen-saturdation group (19.9%) as compared with 107 of 662 infants in the higher-oxygen-saturation group (16.2%)."[34] The rate of severe retinopathy among survivors was higher in the high oxygen group vs. the low oxygen group (17.9% vs. 8.6%).[35] These outcomes led the investigators to conclude that when comparing the lower target ranges to the higher, "there is one additional death for approximately every two cases of severe retinopathy that are prevented."[36] Once the SUPPORT data was published, data safety monitoring committees overseeing similar studies taking place in the United Kingdom, Australia, and New Zealand performed interim analyses using pooled data and halted recruitment for their studies.[37]

Consent Forms

What did the consent forms say about the risks to participants? A systematic review of the consent forms revealed the following:

> Twenty of twenty-two SUPPORT consent forms explicitly or implicitly described the oxygen ranges studied as standard of care, usual care, or as a desired approach in some units.... Eleven consent forms had statements indicating that there was no predictable increase in risk to infants enrolled in the study, and two had statements indicating that there was no more risk to subjects than those seen in premature infants needing NICU management."[38]

In the forms claiming that infants in the study received the "standard of care," some forms explained this was so because the narrower ranges were between the accepted target range of 85% and 95%. Other forms explained that the narrower ranges were sometimes used by NICUs and were considered acceptable. Few forms disclosed the actual NICU target range in use at a particular research site (i.e., the actual "usual care" for infants cared for at that location).

Typical language of the consent forms can be found in the consent form of the University of California-San Diego (UCSD), which served as a template for other sites, and the consent form of the University of Alabama (UAB), the lead site of the study. The UCSD form stated that "[b]ecause all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby." The consent form acknowledged that "some unknown risks may be learned during the study," and stated that "the only other risk of this study is the risk to confidentiality."[39]

In the UAB consent form, the oxygen saturation part of the study is described as monitoring oxygen levels rather than actively managing oxygen levels through reduced or additional oxygen supplementation. The only risk described in the consent form related to the oxygen target randomization is minor skin breakdown. This risk is described in the section labeled "Possible Risks" as follows:

> 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.

This language about the risks of the oximeters themselves, combined with the earlier vague description of

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the study as involving monitoring, could easily have led parents to understand that the part of the study relating to oxygen ranges was observational only. Some parents apparently had this belief.[40] In addition, the disclosures in these forms about risks to confidentiality and minor skin breakdown suggests a thoroughness and complete transparency about all conceivable risks, further conveying the impression that the study was, in practical terms, no risk and that parents did not need to think carefully before agreeing for their child to be a part of the study.

Despite omitting any disclosures of risks from altering infants' oxygen saturation targets, some consent forms listed a possible *benefit* of reduced risk of eye disease for the low oxygen group. In other words, even though investigators hypothesized that the high oxygen group would experience a greater rate of ROP, they did not disclose this possibility as a risk to parents of the infants enrolled in the study. Only a few mentioned a possible increased risk in neurological injury from reduced oxygen, although this was a foreseeable risk of reduced oxygen. None of the forms explained that changing the oxygen ranges at which infants are maintained might affect whether an infant experiences a higher risk of death, although there were well-known and longstanding concerns about such risks, as explained further below.

The SUPPORT controversy is as much about different understandings of "risks of research" as it is about what must be disclosed. In other words, the argument in SUPPORT has not been that research subjects should remain uninformed about reasonably foreseeable risks of research.

OHRP Determination

On March 7, 2013, the Office for Human Research Protections issued a determination letter to the University of Alabama, Birmingham.[41] It did not question the study's merit or its design, although others later would do so,[42] and further serious inquiry and debate about the design and execution of the study are needed. Instead, OHRP, following an investigation prompted by a request from a confidential source, informed UAB that its informed consent form and those of other sites were inadequate because they failed to disclose risks of blindness, neurological injury and death. OHRP's determination letter required UAB's institutional review board (IRB) to develop a plan to ensure that improved informed consent documents include and adequately address the basic elements of informed consent.

Despite this extremely mild sanction, many influential members of the research community protested with editorials published in prestigious medical journals and other venues. NIH officials put pressure on OHRP to back down,[43] which it did, on June 4, 2013, with a second letter to UAB that affirmed the agency's original findings but suspended its compliance action.[44] OHRP explained that there was "widespread misunderstanding" about required disclosure of risks in trials studying standard of care treatments, convened a rare public meeting to discuss and debate the disclosures required by the Common Rule and ethical norms, and has since disseminated, for comment, "Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care."[45] (Final guidance has not yet been adopted.) Despite suspending its compliance action, the OHRP has throughout maintained its essential position on the disclosures required for the SUPPORT Study and for comparative effectiveness research generally.

Question 1: Are Risks from Standard Care Treatments "Risks of Research?"

The Issue and the Stakes

The SUPPORT controversy is as much about different understandings of "risks of research" as it is about what must be disclosed. In other words, the argument in SUPPORT has not been that research subjects should remain uninformed about reasonably foreseeable risks of research.[46] Such disclosures are a requirement of the Common Rule, which clearly applied to SUPPORT. They would be legally required under the common law as well. However, if there are no risks of harm associated with participation in a study, then there are no risks to disclose.

Determining that there were no risks of research in SUPPORT (or in CER generally) would have other implications as well. If there are no research risks, then a study might, under the current formulation of the Common Rule, qualify for a waiver of consent, although such qualification would only be met if "the research could not practicably be carried out without the waiver" and "the waiver…will not adversely affect the rights and welfare of the subjects."[47] (Note that for drug studies, a waiver would not have been permit-

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ted under the FDA regulations in effect at that time.[48]) In fact, some defenders of SUPPORT did argue that a waiver of consent should have been allowed because there were no risks to participation in the study[49] — the position essentially reflected in many of the consent forms with respect to the randomization to high and low oxygen targets.

Altered Care and Risk/Benefit Profiles

This perspective — that the SUPPORT Study did not actually carry any risks of harm — must explain the statement in the letter to the *New England Journal of Medicine* (*NEJM*), signed by 46 self-identified "scholars and leaders in bioethics and pediatrics" who agreed with the proposition that "[a]lthough we acknowledge that the permission forms 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."[50] Since most consent forms (and, in particular, the template and lead site consent forms for the study) did not contain any disclosures of risk relating to changing the oxygen saturation, the authors must have believed that assigning infants to higher or lower levels of oxygen than they would have received in usual care did not carry any increased risks of any harms. But this cannot be correct.

Even assuming, for the moment, that SUPPORT was merely comparing two accepted therapeutic protocols in such common use that other alternatives were not reasonably available, babies in the study would still have faced "additional risks that the investigators failed to disclose." As stated above, the study investigators concluded that babies in the low oxygen group had a higher risk of death compared to babies in the high oxygen group; babies in the high oxygen group had a higher risk of ROP than babies in the low oxygen group. Therefore, babies in the low oxygen group who were cared for in a NICU that, outside the study, targeted the higher oxygen saturation level faced an increased risk of death from that aspect of their participation in the study. A corresponding conclusion follows for risk of ROP for the high oxygen group.[51] These were "risks of research." The children would not have faced these same risks if they had not been enrolled in the study.[52]

It is important to note that this does not mean that any particular infant was actually harmed by being in the study — although they may have been. All it means is that the infants were placed at greater risk of one harm (death) or another harm (ROP) to the extent the oxygen protocol they were assigned to differed from the protocol (or individualized treatment, if available) that would have been followed for them in usual care in the hospital in which they were cared for. To the extent their oxygen saturation target was altered by the study, they also were placed at lower risk of one harm (again, death) or another harm (ROP). The "risks" part of this altered risk/benefit profile were "risks of research" that should have been disclosed under the Common Rule. This seems fairly straightforward.

But, in addition to its general requirement that investigators disclose "a description of any reasonably foreseeable risks or discomforts to the subjects,"[53] the Common Rule contains another provision that defenders of SUPPORT have pointed to as shedding light on the risks required to be disclosed in SUPPORT and in CER generally. This rule, found at 45 C.F.R. §46.111, provides:

> In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).[54]

This particular rule is worth considering as some commentators have urged that it means that the risks associated with the various therapies being compared in a "standard of care" study do not have to be disclosed because the subjects could have received the same therapy outside of the study in the course of usual care.[55] But this is neither the intent nor the plain meaning of this rule.

Because this provision was drafted at a time when comparative effectiveness research on the scale now urged was not contemplated, it should not be read as providing any special insight with respect to such research. Moreover, it relates to IRB assessments of risk rather than the disclosures that must be made to subject-patients. But most importantly, the plain meaning of the provision is to direct IRBs to determine what is different or additional about the interventions patient-subjects would receive in research vs. clinical care. An IRB should determine, for example, whether an imaging scan provided for in a protocol is a scan a patient would normally undergo in usual care or whether it is an additional scan for the purposes of research. If the scan would not normally be done, then whatever risks are associated with it (risks of radiation exposure, for example) would be risks of research and must be calculated in the IRB's assessment about whether the risks to the subject are justified by the potential for benefit to the subject and the knowledge to be gained from the study (the risk/benefit assessment IRBs are required to make).

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Comparative effectiveness research can and usually will change the risk/benefit profile from that which a particular subject would face in usual care. Unless the subjects receive the same care in the research study that they would in usual care, they will encounter "risks and benefits that may result from the research."

This conclusion does not mean that being in a research study on the whole carries more risk of harm than usual care. It may or may not, depending on the study. The actual rate and severity of harms experienced by participants in the different arms of the study will not be known until after the study is completed, but altering an individual's care subjects him or her to different risks of harm.

Risk of Harm vs. Proof of Actual Harm

A number of defenders of the SUPPORT study have called the focus on increased risk of death, in particular, as an instance of Monday morning quarterbacking. It is true that outcomes matter — not to the question of the foreseeability of the risks of harm occurring, but to the gravity of the error of omitting information about them. The fact that babies in different arms of the study had appreciably different outcomes in the aggregate also meant there was a possibility for legal redress through the tort system; without a provable injury — harms that actually manifest — a plaintiff cannot successfully recover in a civil suit for damages even if he or she has been clearly wronged by being denied required information.[56] The U.S. common law system does not generally recognize "dignitary harms" experienced by someone who is denied the opportunity to make an informed decision about treatment alternatives if he or she suffers no physical harm.

Thus far, in relation to the SUPPORT Study, the requirement to prove injury has been an impediment to a successful legal claim by the families of SUPPORT subjects. A federal court recently granted a summary judgment motion of the defendants, SUPPORT investigators and IRB members at UAB, because the plaintiffs could not prove that the infants' participation in SUPPORT caused them injury.[57] The difficulty plaintiffs would have proving injury in this case was clear from the beginning because the *harms* the babies were at risk of (namely, eye disease, death, neurological impairment, lung disease) were the same as the *harms* they faced from their extreme prematurity and/or the interventions, such as supplemental oxygen, they would have received in clinical care because of their prematurity.[58] While the *probability* of those harms occurring for any individual baby was likely altered by study interventions, increased risk alone was not a cognizable injury under Alabama law. Importantly, then, the court's opinion did not address the question whether plaintiffs did in fact face greater risks of harm due to their participation in the study.[59] Nor did the court's opinion address the duties owed by the investigators to the plaintiffs, such as duties to disclose risks of research.

A far different result might be possible in a case involving a study in which investigators compared two different common interventions that had risks of clearly distinct harms. Consider, for example, a study comparing surgery to physical therapy to treat an injury; if risks uniquely associated with the surgery were experienced by a participant randomized to surgery, he or she would find it easier than SUPPORT participants to prove a claim based on failure to disclose those risks prior to enrollment in the study.

Reasonable Foreseeability

But was the increased risk of death foreseeable? Whether one is making out a negligence claim in court or determining whether the requirements of the Common Rule have been met, it is only "reasonably foreseeable" risks that must be disclosed. What makes a risk "foreseeable?" NIH director Francis Collins and two other NIH officials wrote in the *NEJM* that, with respect to SUPPORT, "the increased risk of death was a significant and unexpected finding of the study."[60] They and others ask, how could the risk be disclosed if it was not expected?

But "expected" is not the same as "foreseeable." Risks of harm are foreseeable when (but not only when) one of the purposes of the study is to determine the existence, likelihood, or magnitude of such harms. As a second group of scholars in bioethics and medicine wrote in a counter-letter to the *NEJM*, although "the outcomes were not known ahead of time…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."[61] The draft OHRP guidance similarly notes:

> If a specific risk has been identified as significant enough that it is important for the federal government to spend taxpayer money to better understand the extent or nature of that risk, then that risk is one that prospective subjects should be made aware of so that they can decide if they want to be exposed to it.

In response to this line of argument, some defenders of the SUPPORT Study have argued that the investigators were not studying the comparative risks of

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mortality in the two arms, saying that death was noted in the study only because "death was part of [the] composite endpoint to avoid misestimation of the risk of ROP, since ROP can't be determined in children who die."[62]

The SUPPORT protocol is oddly opaque and vague on the issue of what exactly the purpose of the study was, which might help explain why so many IRBs missed the problems here.[63] But there is ample evidence that the investigators were studying risk of death and, whether they were or not (and whether their study had the statistical power to effectively do so[64]), it is clear that they should have been concerned about the mortality risks of too little oxygen. The OHRP details some of the evidence for this conclusion in its June 4, 2013 letter, including prior studies, discussions among investigators when designing SUPPORT and related studies, and the 2005 statement of the investigators themselves as to purpose on clinicaltrials.gov., which explained that the study "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants."[65]

Moreover, it is important to remember that the standard for which risks must be disclosed — reasonable foreseeability — is an objective not a subjective one. The question is not what risks of harm are already known to exist in a particular study — if the frequency and severity of those harms were known there would be no need to do the experiment. The question is also not what risks the investigators have in fact foreseen or what they expect or whether they are surprised or not at the results of their study. The question is what risks were reasonably foreseeable — i.e., should have been foreseen. There were well-documented and much discussed concerns within the medical community about lower oxygen saturation prior to the study.[66] Describing the need for a large trial to determine the appropriate concentration of oxygen for premature infants, Cole et al., wrote in 2003, "We do not yet know if potentially clinically important reductions in retinopathy may offset increases in other potentially competing outcomes such as mortality or neurodevelopmental/neurosensory disability."[67] The authors also noted that, for such a trial, there may be difficulty recruiting units because, "Some units regard SpO2>90% [the higher oxygen range] as mandatory." The investigators knew this, as they cited Cole and other studies revealing such concerns in their protocol, even if they did not highlight them.[68] But even if they hadn't had actual knowledge of such concerns, they would, under an objective standard, be held responsible for that knowledge.

Question 2: Does Uncertainty about Which Arm of a CER Is "Better" Mean There Are No Risks of Harm to Participation?

As we have seen, one cannot conclude that there are no risks to research simply because a patient might have been offered in clinical care the same or similar treatment that is being studied in one arm of a CER study; care is altered for research purposes, potentially altering the risks to which the patient is exposed. Deciding between offered treatments in clinical care — with the associated risk/benefit profiles of alternative treatments or even no treatment — can be a highly important decision for patients.[69] That is why medical informed consent requires disclosure of the material risks and benefits of those alternatives; research informed consent requires no less and generally more.

Known vs. Unknown Risks

But a second major argument for reduced disclosures for CER is based on *uncertainty* about usual care rather than *similarity* to usual care. It goes something like this: physicians frequently offer one treatment option over another — say one asthma medication over another — for reasons other than any evidence (because it does not exist) that the chosen treatment will be more effective or have fewer side effects than another commonly prescribed treatment. In these situations, the argument goes, the physicians are not subjecting their patients to any risks by choosing one or the other treatments because they do not and cannot know which is better, and the same would be true whether physicians choose between treatment options on the basis of their habit, their medical school education, a drug's inclusion on a formulary or *through randomizing patients in research study*. According to David Magnus and Ben Wilfond, there are no risks to being in such a study because, at the outset of the study, the risks are unknown. They write:

> Before the actual study determining which drug (if any) is better, there is no difference in the risk of each of the arms (and no difference in the risk of being in research versus standard care). In other words, if the relative risks and benefits between two treatments being studied are *unknown*, the risk of the research is 'minimal,' if any.[70]

These authors confuse *knowledge of risk* with risk. In the SUPPORT Study, children in the low oxygen group faced a higher risk of death than children in the high oxygen group, even though at the outset of the study, the investigators did not know there would be more deaths in the low oxygen group. The Study discovered

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and quantified the risk, but the risk from low oxygen existed regardless of knowledge of it.

Clinical Equipoise

If we were to understand, as Magnus and Wilfond urge, that risk only exists when it is known, then we would also have to say that studies involving unproven or experimental interventions are minimal or no risk. No one appears to be arguing that a Phase II trial of an unapproved drug, however, is minimal or no risk, for reasons that are obvious — the drug has not yet been adequately tested for safety or effectiveness.

The argument of Magnus and Wilfond, appears based on a mistaken understanding of the consequences of "clinical equipoise." Others have expressed views similar to theirs; Drazen, et al., for example, criticized OHRP's determination that the consent forms were inadequate "because it [did] not take into account ... the extent of clinical equipoise at the time the study was initiated and conducted."[71]

Uncertainty about the comparative safety and effectiveness of a study drug over existing treatment — the idea of "clinical equipoise" — has long offered clinician researchers a way to reconcile their clinical duties to advance their patients' best medical interests with enrolling them in research. Clinical equipoise, as originally defined by Benjamin Freedman, exists when "there is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the comparative therapeutic merits of each arm of a clinical trial."[72] When clinical equipoise exists, physicians can be understood as fulfilling their fiduciary duties to their patients when enrolling them in research because they do not know which course of treatment is superior.

But clinical equipoise does not mean and never has meant that nothing different will be happening in a research study of importance to the patient or that the risks to which the patient will be exposed do not differ from usual care. It has never meant that a research study carries no risks. Uncertainty about risk has never equated to no or minimal risk. Just because doctors do not know how and to what extent the risk/benefit profiles of two arms of a study differ does not mean they do not differ.

Comparative effectiveness research is no different. As discussed above, for many subjects in randomized comparative effective research, care will be altered in ways that change the risk/benefit profile to which the patient is exposed. Unless the risk/benefit profile of both treatment arms proves to be exactly the same, then there are risks to being in the study. (There may also be potential benefits.) Perhaps some CER trials will turn out to be minimal risk — because the treatments are so similar to one another that they only differ in very minor ways, but there is no reason to believe many or most are.

It is not enough for investigators to say vaguely to potential subjects that they don't know which treatment is better. It is also not acceptable for them to describe the purpose of their study — in either the protocol or the consent form — as simply trying to determine which treatment or intervention is better or superior or the like. Is it better in what way? Because it carries a lower risk of mortality? Because it carries a lower risk of eye disease? Because it carries a lower risk of eye disease without carrying a higher risk of mortality?

What Should Be Disclosed?

It is not enough for investigators to say vaguely to potential subjects that they don't know which treatment is better.[73] It is also not acceptable for them to describe the purpose of their study — in either the protocol or the consent form — as simply trying to determine which treatment or intervention is better or superior or the like. Is it better in what way? Because it carries a lower risk of mortality? Because it carries a lower risk of eye disease? Because it carries a lower risk of eye disease without carrying a higher risk of mortality?

OHRP's determination letters and its draft guidance provide reasonable answers to the question, what should be disclosed? Generally, any study that randomizes subjects to different interventional arms exposes subjects to risk/benefit profiles that may differ from what they would be subjected to in usual care. Those

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harms may be of the same type (as in SUPPORT) or a different type (as in the surgery vs. physical therapy example). The risks and benefits of the treatments being studied, as well as other reasonably foreseeable risks, must be disclosed. If there is a potential benefit to being in one arm of the study (e.g., decreased risk of ROP), there is a potential risk of harm to being in the other arm (e.g., increased risk of ROP). As Mark Schreiner has noted, "Superior efficacy could come at the price of greater risk of adverse events; superior safety could come at the price of diminished efficacy."[74] Potential subjects must be given adequate information to evaluate these potential trade-offs between risks and benefits, understanding that if they enroll in a randomized trial, they will be giving up the opportunity to choose the trade-off they might prefer.

Some members in the research community have argued against the need for disclosures of risk in CER for fear that consent forms and research study coordinators will recite long lists of remote risks for each interventional arm when it is not expected that a significant difference between treatment arms will be discovered. It is true that the way informed consent forms are written today bears serious scrutiny. Many forms go overboard in ways that suggest investigators or institutional sponsors may be less focused on trying to inform potential subjects about the research study and more on trying to cover every conceivable basis for a lawsuit. Routinely including "death" in an alphabetized list of fifty potential risks and for both arms of a study does not truly help potential subjects understand what is at stake in enrolling in a research study. Defensive, exhaustive lists of remote risks can also make enrollment in a study appear to be riskier than it is.

At the same time, there is no reason to exclude information that may be important to potential subjects — even if the risk of harm applies to both treatment arms and there is no reason to suspect a difference in the frequency of that harm occurring. Providing this information would be especially important when the patient-subject has not already been prescribed one treatment or another, or one drug or another, as would be the case for a newly diagnosed condition, because he or she would not already know the risks and benefits of either of the treatments proposed.[75] The challenge in comparative effectiveness research is to bring forth for the consideration of potential subjects the risks of taking either drug (which they would experience in usual care) and the risks of enrolling in a study to compare them. It seems that one reasonable proposal would be to include the risks of harm of taking Drug A and Drug B in an appendix, while highlighting in the main part of the consent form information about the risks of harm that are being studied, or for which a difference in frequency or severity is otherwise reasonably foreseeable.[76] (Such disclosures would need to include risks not just of side effects but that one drug may be less effective than the other.) But this suggestion needs further consideration. While such a manner of disclosure may satisfy the requirements of research consent, if the researcher is also acting as the patient's doctor with respect to the treatment offered in the study, the researcher-physician would need to discuss thoroughly the material risks of taking either drug and any other alternative courses of treatment (including no treatment).

There are, to be sure, other ways to improve the readability of consent forms while also pointing out to potential research subjects the risks associated with the research. More work on this is needed.

Attention should be given, for example, to the tendency for informed consent forms to be divided into discrete and rigid disclosure "boxes" so to speak — for example, a list of risks, the right to withdraw, etc. We would do well to think less about *categories* of disclosure and more about the *purpose* of disclosures. That purpose is to enable potential subjects to make informed choices about whether to enroll in a study. The current regulations, therefore, require disclosures about more than risk. They require, among other things, an explanation of the purpose of the experiment as well as the procedures that are being studied and the alternatives available to the patient-subject. All of these disclosures work together. Isolation of "risk" makes it easier to lose sight of the goal of the consent documents and the consent process associated with them. It would be more helpful to adopt a *transparency* model of consent for research similar to the approach Howard Brody has advocated for informed consent processes in clinical care.[77] The transparency model would aim to make transparent to potential subjects the thinking of the investigators. What do they think they know? What is commonly believed? What exactly are they studying? Why did they choose this study design?

Had SUPPORT investigators been transparent in the consent process, the parents would have been much more fully informed about the risks and potential benefits to research participation for their infants. In SUPPORT, parents should have been told, at a minimum, how the care their babies would receive in the study would differ from the care they would receive if not enrolled in the study; the study's purpose; and that there were concerns within the clinical community that the higher oxygen levels might be associated with an increased risk of blindness, and the lower levels, with an increased risk of neurological injury and

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death.[78] Parents should not have been led to believe that they were enrolling their children in a minimal risk study, implying that there was no need to think hard about enrolling or to ask important questions.[79] They should not have been told that their children would receive standard of care, implying that their baby's care would not be altered by research participation. Such an impression was not only inadequate, it was false.

Distinguishing CER from Other Types of Studies

Finally, there may be good reasons to call a research study "comparative effectiveness research" or a "standard of care" study, but doing so does not relieve investigators or IRBs of the duty to carefully scrutinize the risks involved in a study or to ensure that those risks are disclosed to potential subjects. Thinking it does leads to inadequate protection of human subjects.

This also can be illustrated with SUPPORT. Even though controversy about the study sparked the current debate about what disclosures are required in CER, it was not itself a "standard of care" study. Most obviously, using untested altered oximeters to show incorrect readings of infants' oxygen saturation levels is not standard of care. But NICU practice in the U.S. in the early 2000s was also not divided between the low and high oxygen protocols. A recent comprehensive study of English-language articles on usual care oxygen management in extremely premature infants concluded that:

> While the high oxygen saturation target range (91 to 95%) was consistent with usual care, the low range (85 to 89%) was not used outside of the SUPPORT trial according to surveys and clinical studies of usual care. During usual care, similar lower limits (< 88%) were universally paired with higher upper limits (> 92%) and providers skewed achieved oxygen saturations toward the upper-end of these intended ranges.[80]

The likelihood that infants outside the study would have been intentionally maintained at the lower oxygen target range was very low. SUPPORT was not actually comparing outcomes between patients receiving different treatments in widespread use. It was not CER.

The fact that SUPPORT has been repeatedly and incorrectly labelled as CER reveals one of the dangers of treating CER differently, of assuming that it somehow lightens review and disclosure obligations. If the label is wrong, the review is wrong.

But even if the label is right, even if a study does simply compare treatments in widespread use, there are no ethics review shortcuts for CER. For each CER study, as for any other study, investigators and IRBs must specifically review each of the treatment arms and carefully consider the risks that should be disclosed. The interventions a subject receives in a CER study might carry different *types* of harms and/or different *rates* of the *same* harms. They might be more or less effective is treating a patient-subject's medical condition. They might align more or less well with the preferences and values of patient-subjects.

Conclusion

Much of the current debate about SUPPORT and about comparative effectiveness research has been focused on how minimal the disclosures can be.

Rather than asking how little must be disclosed — rather than searching for the minimum allowed — we should be *asking what is the best we can do?*

Note

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