

Research on Medical Practices and the Ethics of Disclosure

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In March 2013, the Office of Human Research Protection (OHRP) issued a finding against the University of Alabama and other institutions for failing to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks during the conduct of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial.¹ This study compared 2 different target oxygen saturation levels that were part of usual practice in extremely premature infants. As a result of public disagreement regarding whether the differences in outcomes should be considered a “research risk,” OHRP suspended the determination and held a public hearing in August 2013.²

On October 24, 2014, the OHRP released draft guidance, for public comment, on disclosing reasonably foreseeable risks in research evaluating “standards of care,” which on the surface, seems to be a reasonable approach.³ But a more careful analysis reveals a view that may hinder research without increasing protection of participants. The OHRP draft guidance mischaracterizes the purpose of research, which we agree should be disclosed to participants, as risks of research. The OHRP draft guidance misidentifies minimal-risk research as greater than minimal risk. This will result in requiring misleading information in the informed consent process by making research sound riskier than it really is. This will be particularly problematic for pediatric research, as parents and institutional review boards (IRBs) need sound advice to protect children from risky research and to encourage ethically acceptable research that is important to improve child health. We suggest a number of changes should be made before any guidance becomes finalized.

First, OHRP should not use the terminology of “standard of care” research. “Standard of care” is a legal construct to define a floor of treatment below which claims of negligence are appropriate. To better capture the range of research on the array of usual practices that are studied to resolve clinical dilemmas above that floor (including observational studies using medical record review, randomized clinical effectiveness research, and cluster randomization) we suggest using the term “research on medical practices.”

Second, OHRP should not consider the purpose of research to necessarily be a risk of research. The OHRP argues that if some of the participants in a research study receive treatments that are different from what they

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would otherwise have received, then the risks of that treatment are research risks. Further, they argue that if the research is being undertaken to evaluate the relative risks and benefits of 2 or more common medical practices, then the purposes of the research are also research risks.

Suppose investigators are doing a randomized comparative effectiveness trial of 2 common asthma medications in children (inhaled corticosteroids) with similar side-effect profiles. There has been limited research in children with asthma comparing these medications and clinicians are unsure which drug is more effective at preventing serious complications of asthma exacerbations, including missed school days and hospitalizations, and which has higher rates and severity of the known side effects.⁴ Some clinics may routinely include only 1 medication on the formulary, and other clinics allow providers to prescribe either. Given the lack of evidence to support a preference for one drug over the other, we might suppose that the primary factors determining pediatricians' preferences are exogenous factors (eg, geography, relationship with particular drug detailers, personal experience). According to OHRP, because what treatment a particular child gets may be different from what they would otherwise have received, it is necessary to think of the possibility that a child may get a treatment that has greater rate or severity of side effects or higher rates of asthma exacerbations (because it is less effective) as research risks. And in addition, such research is more than minimal risk (because an increased risk of asthma exacerbation is greater than minimal risk).

Yet, any child not enrolled in the study who received an inhaled corticosteroid for asthma would be exposed to similar probability of increased rates of disease or side effects. It may turn out that one of the

drugs is safer or more effective than the other. And it may be that some of the children who received the less effective or more harmful medication would have received the better drug had they not enrolled in research (and thus experienced harm by being enrolled). Similarly, there are other children who will turn out to have experienced benefit by enrolling. But these experiences do not mean that there were any differences in risk or benefit of the research. 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).

The OHRP has confused risk, which is the product of the probability of harm and its magnitude, with uncertainty.⁵ In the previously mentioned scenario, there is no difference (before the study) in the risk of being in research versus not being in research, because the 2 drugs have a similar probability of being better treatments or having fewer side effects. Further, saying that parents need to be told that they are exposing their child to increasing risk of asthma exacerbations (or higher rates or severity of side effects) is misleading. Children whose parents choose not to enroll them in research will still be exposed to similar probabilities of harm in clinical care as they are in research. Assigning a treatment as part of research as opposed to a decision by the pediatrician does not change the risks of the treatment into research risks unless the risks substantially differ from what the child would be reasonably expected to be exposed to in usual treatment. The problem in describing this decision as potentially harmful is that it can convey a sense of moral culpability by the parent, clinician, or researcher that should have been avoided. Even once there is greater certainty that one medication is better, it does not mean any of these were responsible for harming children when uncertainty was present.

There are many aspects of research that need to be explained to parents (unless there is a waiver or alteration of consent). These include the purpose of the research and in what ways their treatment assignment will differ from what would otherwise take place (eg, by randomization rather than by pediatrician choice). There may be other differences between the arms of a comparative study that parents would want to know about, even in the absence of a difference in risk.⁶ For example, a study comparing 2 treatments, one with a small probability of a great harm, the other with a great probability of small harm, might present the same level of risk. But parents may assign very different utilities or have very different assessments of the 2 arms depending on their values and preferences.

Our view is that in evaluating risks (and the level of risk associated with a study) the key issue is the one spelled out in 46.11(a)(2) of the common rule; namely, that "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)."⁷ This means that in evaluating the level of risk of a trial, the relevant consideration is whether there are differences in the probability or magnitude of harm as a result of being in a trial versus not being in a trial.

There are two reasons why OHRP's position is problematic. First, by claiming that research is more than minimal risk even if there is little difference in the actual risk of being a participant versus not being a participant in research, IRBs and investigators would be stripped of important regulatory options that may be necessary for valuable pediatric research to take place. Alternative approaches to informing parents about research may require waivers of documentation or waivers

or alterations to normal consent requirements, which require a finding that research is minimal risk.^{8,9}

Second, OHRP's draft guidance would unnecessarily make research sound riskier than it really is. If there were no difference in risk (ie, the product of the probability and magnitude of harm) as a result of being in research versus clinical care, the guidance would mislead parents by misinforming them of the risks of enrollment. If investigators and IRBs exaggerate risks, it could make it harder to recruit children into valuable research. More importantly, parents may misattribute unavoidable risks of clinical care as avoidable research risks.

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