

critical in implementing successful prevention and control activities. The detection of human H7N9 virus infections is yet another reminder that we must continue to prepare for the next influenza pandemic. The coming weeks will reveal whether the epidemiology reflects only a widespread zoonosis, whether an H7N9 pandemic is beginning, or something in between. The key is intensified surveillance for H7N9 virus in humans and animals to help answer important questions. We cannot rest our guard.

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## Risk, Consent, and SUPPORT

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Comparative effectiveness research has the potential to dramatically improve patient care while reducing costs. In the absence of good evidence about which treatment is best for particular patients, decision making too often hinges on exogenous factors such as advertising and detailing by pharmaceutical companies, what a physician first learned to do, insurance coverage, and local custom. Without good evidence about what is best among competing but generally accepted clinical options, it is often a challenge for physicians to identify the best course of care.

A great deal of effort is under way to make it easier and less expensive to conduct prospective, randomized comparative effectiveness research.<sup>1</sup> Some of the options for conducting such research take advantage of the fact that there is no additional risk to being randomly assigned to one or another equally well-supported treatment option that falls within the stan-

dard range of care in clinical practice. This all seems for the good, but there is cause for concern in a recent decision by the Office for Human Research Protections (OHRP) to issue a letter of determination to investigators at the University of Alabama at Birmingham (UAB) about a large multicenter clinical trial to determine appropriate oxygen-saturation levels in severely premature neonates.<sup>2</sup> The OHRP reprimand is troubling both because it has sown confusion and focused unwarranted negative attention on valuable research and because it incorrectly suggests that the risk of comparative effectiveness research involving infants, or any other group, is equivalent to the risk of research involving randomization to a novel intervention.

The UAB case concerns a trial undertaken to determine the appropriate oxygen-saturation levels to use in very premature infants. Among neonatologists, the standard of care varied — too much

oxygen was associated with retinopathy of prematurity and possible blindness, but too little oxygen risked neurologic damage and death.<sup>3</sup> By the mid-2000s, neonatologists were calling for research that would help clarify the best oxygen-saturation levels for these patients.<sup>4</sup> Many believed that lower levels would reduce the incidence of retinopathy of prematurity without increasing mortality. The trial, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), randomly assigned patients to higher and lower oxygen-saturation levels within the standard of care.<sup>5</sup>

The OHRP has now found fault with the consent language used when patients were enrolled in SUPPORT. We think it is important to be very clear about the issues at stake here. One is about risk, and the other is about informed consent.

The SUPPORT investigators believed that since all the study infants would receive oxygen levels

within the prevailing standard of care, there was no additional risk to being enrolled in the trial. Indeed, it has been argued that the research should have been eligible for a waiver of documentation of informed consent, since there was no basis for claiming an increase in risk from enrolling in the trial versus receiving standard clinical care.

Before the study began, there was insufficient evidence to know what oxygen level within the guideline-specified range was best. 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. The first problem with the OHRP letter and a good deal of the public outrage that followed is the confusion of the risks of the clinical treatment with the risks of the randomization. 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.

The OHRP suggested that even though any individual physician could approve settings at either the higher or lower oxygen target while still operating within the standard of care, there might be additional risk because patients were typically allowed to range across the entire spectrum rather than being limited to a narrower band of oxygen-saturation levels. Not only is there no evidence to support the idea that this increases risk, but the study also included a nonrandomized case-control group that showed that patients enrolled in the study did better

than patients who were not enrolled. Although that finding is not definitive, there is absolutely no evidence to support the claim that the infants enrolled in the study were exposed to greater risk than infants outside the study.

The second issue involves informed consent. The OHRP finding that the researchers failed to adequately inform the infants' parents is grounded in the mistaken assumption that there was an increase in risk to being enrolled in the trial. In terms of substantive informed consent, the parents were given the information they needed to make an informed decision and were in fact offered more information than parents are typically given regarding the care of premature newborns. The consent documents state clearly that there is randomization, that the randomization is to specific oxygen levels, and that there is some evidence of a risk of blindness with higher oxygen levels. And this is, of course, all taking place in a clinical context in which parents understand that the standard treatments may be unsuccessful and that there is a grave risk of death. In other words, parents were provided with the relevant information they needed to make informed decisions about study participation. The OHRP's objection lacks merit, since it refers to the true claim that the randomization itself introduced no further risk than the standard of care.

Those in charge of oversight of human-subjects research, such as institutional review boards and the OHRP, have solemn responsibilities. On the one hand, they are charged with protecting participants in human-subjects research. This means ensuring that risks are minimized as much as possible and are reasonable rela-

tive to the benefits of the research and — for most studies — that patients or their surrogates provide informed consent before enrollment. On the other hand, those responsible for oversight must be mindful of the value of important research. Those charged with oversight must discharge that obligation by ensuring that measures that may impede the conduct of valuable research genuinely offer substantive protection to participants.

With regard to SUPPORT, the OHRP is asking that research be described as riskier than it really is and is suggesting that the parents were duped into enrolling their frail infants in dangerous research. Not only is that not true, but it also poses substantial risk to the conduct of valuable comparative effectiveness research both for premature infants and for the general public who continue to face too many treatments where uncertainty prevails about what is best.

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