VIEWPOINT

Comparative Effectiveness Research
Ethical and Regulatory Guidance

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In March 2013, the pediatric research community was rocked when the Office for Human Research Protections of the Department of Health and Human Services determined that the informed consent documents in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a National Institutes of Health–funded, Neonatal Network multicenter study, failed to include, or adequately address, basic elements of informed consent as required by Health and Human Services regulations. A firestorm of controversy ensued and continues to this day.[1-3]

This controversy is part of a larger critique that holds that the current US regulatory framework for governing protection of human research participants is an impediment to comparative effectiveness research (CER), which aims to compare 2 "usual" or "standard" treatments. Thoughtful commentators point out that research that collects data at the point of care, or compares different forms of care delivery, blurs the traditional distinction between research and treatment and is not a helpful guide to managing the oversight of such activities.[4] Some have called for major revision of the extant regulations.[5]

This debate raises a number of questions: How should we assess risk in CER studies comparing 2 interventions, both of which are considered usual or standard? Does randomization increase the level of risk to subjects? Should randomization always require informed consent? And finally, are current federal regulations that govern research appropriate for CER? We address each of these questions.

How Should We Assess Risk in CER Studies?

Level of risk should be determined by the incremental risk imposed by the research itself, not the level of risk inherent in the treatments being compared. The level of risk in CER is often minimal, since both arms offer interventions known to be efficacious. However, there may be times when the 2 usual care arms have differing levels of risk, making the incremental risk of being in the study more than minimal. More than minimal risk does not preclude children from enrolling in such studies; it merely obligates the use of informed consent (and assent when appropriate) and evaluation of the study by the institutional review board (IRB) as one in which there is the prospect of direct benefit.

Further, many "standard" treatments are not, in fact, validated. They represent customary practice but may have little or no evidence base. One should use caution in describing the 2 arms of a CER study, reserving the term *standard* only for those treatments for which evidence of efficacy does exist and using the term *customary* for usual practice not yet validated.

Does Randomization Itself Increase Risk?

In the SUPPORT study, investigators randomized preterm newborns to receive either high or low oxygen saturation settings to determine the impact of lower levels of oxygen saturation on the development of retinopathy of prematurity. Importantly, both the high and low levels remained within a range (>85% saturation and <95% saturation) that is widely accepted in neonatal practice. The investigators argued that they were simply comparing 2 "standard" treatments.

The Office for Human Research Protections criticized SUPPORT's consent documents because they only mentioned the potential benefit of reduced retinopathy of prematurity for babies at the low oxygen level but did not mention the correlative risk of potentially increased retinopathy of prematurity for babies at the high oxygen level. When investigators hypothesize differential outcomes in each arm of a study, consent documents should explain both the benefits and risks of each arm.

Should Randomization Always Require Informed Consent?

In most cases, randomization at the level of the patient should require informed consent, even when 2 Food and Drug Administration–approved medicines or 2 kinds of health care delivery interventions are being compared. Consent should be sought, not because one arm of the study may be any riskier than the other, but because patients and their surrogates may differ in their preferences and beliefs, and respect for their personhood requires that we allow them to make a fully informed decision about participation. However, consent should be waived when there is minimal risk in both arms of the study, seeking consent would make the research impossible, and the differences between the arms are not meaningful to patients or are the very thing being studied. For example, consent could be waived if patients were randomly assigned to 2 kinds of low-risk medical adherence interventions, one using computer-based reminders and the other telephone calls.

Cluster-randomized studies that randomize at the unit or organizational level raise other questions. Here, seeking consent is far more difficult, could render many studies logistically impossible, and presumes more choice than patients actually have since they often have no ability to change physicians, units, or institutions where they receive care. Yet cluster-randomized studies are often the best way to test the effectiveness of new patient care interventions, because they allow for robust organizational "uptake." When randomization occurs at the patient level, rather than unit or institutional levels, health care professionals worry about contamination and therefore restrain their behavior, blurring dif-

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ferences between the 2 arms of the study, and investigators cannot deploy broad cultural change techniques to encourage new health care professional and patient behavior.[6] Thus, cluster-randomized studies offer great benefits. If neither arm introduces more risk than patients would likely experience if no study were planned, then individual consent should be waived.

Are Current Federal Regulations Appropriate for CER?

Yes. The problem is not the current regulatory framework but its overzealous application by IRBs. Given the urgent national need to improve health care, and the great promise that CER holds for doing so, the human research participant protection process must not be an impediment.

We agree with critics of the current research participant protection framework that the research-treatment distinction blurs in CER and in other forms of research on care, but that reality still leaves the question of how best to provide oversight. Some entity must determine likely levels of risk and benefit and whether consent is needed or can be waived. Institutional review boards are the natural institutional home for these determinations. But too often, IRBs and their hospital administrators and lawyers impose complex and incomprehensible consent forms on research subjects, focused more on eliminating institutional risk than protecting research participants.

Existing federal regulations allow for the flexibility that CER requires and clearly state that local IRBs may "alter, some or all, of the elements of informed consent…or even waive the requirements," if the research involves no more than minimal risk to the subjects, the waiver will not adversely affect the rights and welfare of the subjects, and the research could not practicably be carried out without the waiver.[7] Local IRBs should be held accountable for developing the necessary expertise to appropriately review CER and monitor it in ways that are not excessively burdensome.

Conclusions

We call on local IRBs to educate themselves about CER, use their authority to exempt low-risk CER studies, help researchers develop better and less complex informed consent forms, and offer waivers of consent, when appropriate. We also urge institutions involved in multisite studies to develop and use centralized IRBs to further reduce oversight burdens on investigators. For its part, the Office for Human Research Protections should develop guidance for IRBs, including examples of CER protocols with varying degrees of risk, and explanations of how current guidelines can be interpreted to offer the right level of oversight. Only by working together can researchers, regulators, and local IRBs use the powerful assets of CER to improve the quality of US health care.

ARTICLE INFORMATION

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