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POLICY FORUM
Legal and Ethical Policies Regarding Research Involving Critically Ill Children
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Parents who have children in the pediatric emergency department (PED) or pediatric intensive care unit (PICU) are under great stress; they are worried about the safety and health of their child, and they are asked to make medical decisions in a short time, sometimes with little information, and many times with unfamiliar physicians. Parental anxiety is increased when discussions of research enter the conversation. This paper examines the legal framework for research in pediatric emergency medicine and critical care and then looks at some of the ethical dilemmas that occur in research with critically ill children.

Legal Issues
The Department of Health and Human Services (DHHS) has established a set of rules for the protection of human research subjects that is codified in the federal register (45 CFR) [1]. Subpart D refers explicitly to pediatric research subjects. This section describes the rules an institutional review board (IRB) must follow when reviewing research involving children. First, it must ensure the following guidelines are met: (1) the risks to subjects must be minimized; (2) the risks to subjects are reasonable in relation to the anticipated benefits, if any; (3) subject selection is equitable; and (4) informed consent is obtained in a manner appropriate to the risks of the research.

The regulation then discusses risk levels and who must consent or assent to research projects that pose varying levels of risk and benefit. Minimal-risk research does not cause any foreseen potential harm to the child participating and includes those activities a child might do during a routine well-child visit or in daily life, such as play video games. All children can participate in this form of research and only one parent needs to consent. In most of these studies, a child 7 and older would also assent to participate.

The next level is research that offers the prospect of direct benefit to a subject and poses more than minimal risk. This form of research involves children with a disease or condition that might be improved or treated with the drugs, procedures, and devices that are part of the trial. This research requires one parent’s consent and, in some situations, assent from the child. Many institutions waive the requirement of assent if the drug, device, or procedure is available only through the research protocol.
Finally, if a child is asked to participate in a trial that poses more than minimal risk and offers no direct benefit but will produce generalizable knowledge about a disease or condition that the child has, then both parents must consent. This may be a phase-1 drug study, genetic research, or tracking a tumor’s progression by using sedated MRIs. Only children who have the disease or condition in question can participate.

Sometimes, pediatric emergency and intensive care physicians want to do emergency research, that is, research carried out when consent is not possible, such as during an attempt at resuscitation. This type of research falls under the emergency exception from informed consent (EFIC). EFIC requires that the subject have a life-threatening condition, available treatments are unproven or unsatisfactory, and informed consent is not possible because of the urgency of the situation [2]. Further, the risks and benefits to the subjects must be reasonable, and there must be a prospect of direct benefit to the individual. Lastly, the researcher must verify that there is no other way the research could be done.

If these criteria are satisfied, the researcher must obtain permission from the FDA, consult with community leaders, give a public disclosure in the community through newspapers, flyers, radio, or TV about the risks and benefits of the research prior to starting the project and then announce the results in the same manner at the end of the study. Finally, the subject and family must be told that the subject was part of the study as soon as possible. If the study has additional parts that continue after the family’s notification, then the family or subject must have the ability to opt out of these as long as stopping the research early does not place the subject at risk of harm.

**Ethical Issues**

While the legal guidelines are straightforward, gaining approval for research studies in the pediatric ED or ICU can be complicated by the informed consent process. Parents of sick children in an emergency room or intensive care unit are under immense emotional distress and approaching them with a request that their child participate in research may only increase that distress. Nevertheless, the parents must understand the research sufficiently and feel comfortable consenting to it, even though their child may be extremely ill.

Most pediatric emergency medicine and critical care research falls into two categories: studies that pose minimal risk and those that pose more than minimal risk but also the prospect of direct benefit.

*Minimal-risk and quality improvement projects.* Although minimal-risk research and quality improvement projects appear straightforward, an IRB may require that clinicians wait for some period of time after a child’s admission or arrival in the ED to approach a family about such research. The waiting period might last until a diagnosis and treatment plan are determined, just prior to discharge, or after 24 hours in the PICU. These waiting periods may seem to be inconveniences for the researcher, but it is unjust to burden an ill child and family for research purposes alone.
Drug research with a possible benefit to the subject. A research study that offers potential benefit to the sick child can be equally challenging for a parent to consider. If the researcher presents the study appropriately, he or she will say that it is not known whether the study drug offers any benefit over the standard of care and that is why it is being studied. This situation is known as “equipoise” and means that the expert medical community is uncertain of the therapeutic benefit of a study drug or procedure.

Parents of a very sick child often feel pressure to consent to the use of trial drugs because they believe the study offers their child the best chance of recovery or that, by enrolling, the child will get better care from the medical team. Parents may agree to the study, though preferring their child not participate in research.

Research in the PICU and PED also subjects parents to feelings of extreme guilt regardless of their decision. If they do not consent to research, they may feel guilty for denying their children a possible treatment. If they consent, they may feel guilty about exposing their children to a drug that may not help and has risks. Either way, parents are likely to feel uncertain about the decisions and the child’s future. If research were not an option, the parents would consent to standard care, which, though scary, has demonstrated results and risks.

Emergency research. Emergency research compounds these issues. Placing a child in a research study without the parents’ permission denies them the opportunity to make decisions for their child. Parents worrying about their injured child while a physician performs an experimental procedure on the child is ethically problematic. Having to meet parents, discuss the critical nature of their child’s condition, and state that a research drug was used in the child’s initial management can be difficult. Parents may be distressed that no one in the trauma bay told them about the research, that their voices were not sought at the most critical time in a child’s life. They may link a poor outcome to the study rather than the critical condition of the child. EFIC research requires special consideration and oversight and should only be used after rigorous scrutiny of the protocol by the investigator, the IRB, and the community.

Conclusion
Research in the PED and PICU is essential to advance medical understanding of the efficacy of emergency interventions, both drugs and procedures. Yet researchers must be careful to minimize the additional stress that consent and participation in research entail for people in these circumstances. Minimizing distress and risks to the subject and family will ultimately lead to a more successful research experience for everyone, even if the intervention itself is unsuccessful.
References
1. Department of Health and Human Services. Basic HHS Policy for Protection of Human Subjects (Common Rule), 45 CFR part 46 subpart D.

Further Reading


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