Unproven Therapies in Clinical Research and Practice: The Necessity to Change the Regulatory Paradigm

In this article, we challenge two fundamental assumptions underlying the current regulation of research for unproven therapies: (1) current regulatory practices serve the best interests of patients and (2) standard definitions allow clear demarcation and rational regulation of such therapies in clinical practice, research, and quality improvement (QI) activities. Our goal is to prompt serious consideration of how to better serve all patients, not just research participants, treated with unproven therapies. We begin with a depiction of usual perinatal practices in 2009.

Dr Smith, an obstetrician in a major hospital, delivers a 27-weeks' gestation infant who cries at delivery. As part of long-standing clinical practice Dr Smith immediately clamps the umbilical cord. He then hands the infant to Dr Jones, a neonatologist, for additional care. Later that day, Dr Smith performs an emergency caesarian delivery for fetal distress at 38 weeks' gestation. The infant does not breathe immediately. Dr Jones initiates resuscitation using 100% oxygen, a practice widely recommended for decades. Neither Dr Smith nor Dr Jones had discussed early cord clamping or resuscitation with 100% oxygen as unproven therapies with the parents.

Obstetricians and neonatologists in a perinatal center in the same center proposed large randomized trials to assess delayed cord clamping and use of restricted oxygen concentration during resuscitation. However, they abandoned plans for these trials because of difficulty in meeting stringent institutional review board (IRB) requirements for informed consent.

Like many other therapies used in clinical practice, neither early cord clamping nor resuscitation with 100% oxygen ever had proven value by current Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines, US Preventive Task Force Services criteria, or other similar criteria. Systematic reviews now suggest that delayed clamping of the umbilical cord reduces the incidence of brain hemorrhage in preterm infants and indicate that routine use of room air during resuscitation prevents oxidative injury and reduces deaths among term infants, findings that have now changed treatment recommendations, although it is unclear how much usual practice has changed.
This depiction illustrates the following problems:

1. **LONG-STANDING REGULATORY REQUIREMENTS AND IRB POLICIES HAVE INADVERTENTLY DISCOURAGED RIGOROUS EVALUATION AND ENCOURAGED ROUTINE CLINICAL USE OF UNPROVEN THERAPIES.**

Most treatment methods have never been rigorously assessed to ensure their risks do not exceed their benefits. The risks and regulatory barriers are likely to be greatest in circumstances when informed consent is difficult to obtain. Fifteen years ago the National Institute of Child Health and Human Development Neonatal Research Network seriously considered performing a large trial to assess whether delayed cord clamping would reduce major adverse outcomes in small premature infants. Many of the mothers obtain no prenatal care, and any serious effort to obtain valid consent before birth for a high proportion of infants would require research personnel present at all hours in all centers. For that trial, the network investigators concluded that informed consent requirements in their centers would preclude an adequately powered trial of reasonable length and affordable cost that would be free of major selection biases (this despite the fact that immediate cord clamping is routinely used without consent in clinical practice).

Regulatory barriers are also likely to have contributed to the dearth of trials in the United States assessing restricted oxygen administration during neonatal resuscitation and to a large number of avoidable deaths worldwide. Although prompt, meaningful consent may be impossible in emergencies, federal regulations allow emergency exemption to informed consent only when community consultation, public disclosure, and other strict requirements are met. Even then, local IRBs may not allow waiver for any patients, and few trials of emergency therapies continue to be published. Yet thousands of unnecessary deaths may be caused by undue regulatory barriers or consent requirements that reduce enrollment in trials of effective therapies or that obscure their treatment effects due to selection biases or delays in treatment. At the same time, the current regulatory approaches have an unclear basis.

2. **CLINICAL PRACTICE, RESEARCH, AND QI CANNOT BE CLEARLY DEMARCATED AND RATIONALLY REGULATED BASED ON STANDARD DEFINITIONS.**

Clinical practice has been defined as activities designed solely to enhance patient well-being; research, as systematic activities designed to develop generalizable knowledge; and QI, as systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings. Although seemingly straightforward, these and similar definitions are problematic for multiple reasons including the following:

A. **Clinical practice is not designed solely to improve patient well-being.** Factors that influence practice include professional greed, insurance coverage, malpractice concerns, patient demands, and the physician’s stewardship responsibility to use limited health care resources wisely.

B. **Obtaining generalizable knowledge (a better understanding of disease and how to better treat future patients) is an important and inextricable component of practice.** Producing generalizable knowledge, even if applicable only to future patients in the same hospital, is also basic to QI.

C. **Systematic data collection to monitor and improve health care is an important, ubiquitous, and increasing component of good clinical practice and QI.**

D. **The double standard for obtaining informed consent for unproven therapies in clinical research but not in clinical practice is illogical.** Smithells quipped that permission was required to give a new drug to half his patients but not to all. As Fost notes, it is not plausible to presume that a patient would want a therapy never properly tested for safety or efficacy with no previous review but would object to the same treatment with all the safeguards of a controlled trial.

E. **The risk of administering an unproven therapy is not greater in clinical research than clinical practice.** Moreover, the total number of patients harmed from well-meaning use of unproven therapies is undoubtedly orders of magnitude greater in practice than research. Well-known examples in treating preterm infants include administration of sulfonamides and of chloramphenicol to prevent or treat sepsis, a high FiO2 to prevent recurrent apnea, a FiO2 no greater than 50% to treat infants with severe respiratory distress, and, more recently, early high-dose corticosteroids to prevent bronchopulmonary dysplasia. As recently emphasized by Kass et al, “the labels ‘research’ and ‘practice’ are poor proxies for what should be our central moral concerns.”

**WHAT SHOULD BE DONE?**

As noted by Eisenberg in 1977, impeding research, no less than performing it, has ethical consequences. Kass et al and Faden et al have called for a new ethical foundation to facilitate clinical care, QI, and research. Much will be required to develop and evaluate new approaches and the resulting regulatory implications. In our view, informed consent requirements...
should be based on the discernible risk to the patient rather than on ambiguous distinctions between practice, research, and QI. We see no ethical reason why they should differ for patients given the same unproven therapy. This approach would facilitate trials to address such issues as when the umbilical cord should be clamped or how much oxygen should be administered during resuscitation. As recommended by others, enrollment in well designed comparative effectiveness trials should be allowed without informed consent when it cannot reasonably be obtained and risk is not increased above that with the same therapies in clinical practice. Enrolled patients or their surrogates could later be informed of these trials as part of the ongoing effort to identify better treatment methods. However, as for all regulatory practices, the views of patients and the effect of such changes on patient outcome deserve empirical evaluation.

REFERENCES

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