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**EDITORIALS****Minimal risk: The debate goes on\*****Key Words:** medical research; research participants; component analysis; **minimal risk****\*See also p. 1146.**

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Before Nuremberg, Helsinki, and Belmont, there was the Flexner Report ([1](#)), which symbolizes the ascendancy of scientific medicine. Scientific medicine has a responsibility to demonstrate that its therapies for people are as safe and effective as possible. That entails research on people. In acute care, it means research on vulnerable people who need research-based treatment, who cannot authorize their participation, and who have no surrogate to authorize it in a timely way. In a very interesting article in this issue of *Critical Care Medicine*, Drs. McRae and Weijer ([2](#)) address measures to protect this specific population. “Emergency patients,” they say, “are arguably the most vulnerable class of potential research participants. If acute care research is to proceed, emergency research participants must be afforded stringent additional protections.”

Medical research learns its ethics slowly. And sometimes in unspeakable ways. Nearly 40 yrs passed between the Flexner Report and the Nuremberg Code. Nearly another 20 passed before Henry Beecher reviewed ethics problems in biomedical research ([3](#)). Even after Beecher’s essay, the Tuskegee experiment, sponsored by the U.S. government, continued for 6 yrs ([4](#)). The Office for Protection From Research Risks and the Food and Drug Administration continually stop protocols or suspend entire research programs ([5](#)). Some programs have stoutly defended their decisions to authorize the contested protocols. Not surprisingly, a private watchdog organization, the Alliance for Human Research Protection, now looks over the shoulder of official protectors of vulnerable populations.

Protection of human research participants occurs at the nexus of a number of tensions. Medicine itself is an ongoing tension between research and treatment ([6](#)). Research harbors many tensions about valid and reliable research design, investigators’ zeal and ambition, competition, honest reporting of procedures and data, and so on. In medicine there is the need, which is sometimes a temptation, to do good. Ethics contains a tension between established solutions, often called applied ethics, and a responsibility to craft new ethical solutions when they are needed.

The government uses established solutions in protecting research populations. But established solutions can be narrow, narrowly understood, and narrowly applied. Narrowness can transform established solutions of ethics into sources of harm—even evil—for the very people they were intended to protect. Furthermore, we are always learning about the

social technology that is a contribution of ethics to good decision making concerning research and treatment. Biomedical research ethics is very complex.

One established solution for protecting human biomedical research participants requires voluntary participation, administered as informed consent. That requirement stands at odds with the needs of certain classes of patients who require research-based advances in treatment.

Reviewing various efforts to ensure consent by decisionally incapacitated, acute care patients who lack surrogates, Drs. McRae and Weijer ( [2] ) conclude that informed consent is neither necessary nor sufficient to protect patient interests. For “vulnerable populations ... protections afforded by the principles of justice and beneficence become particularly important.”

For good reason, in justifying acute care research on this population, the authors do not start with autonomy. This population cannot consent. Rights-based justification of research on these people should protect their right to life. Emergency research involves a tragic choice ( [7] ) between two values, neither of which can be willingly relinquished: predicating research on informed consent vs. trying to preserve life and function.

In the mid-1990s, however, regulators of research on acute care patients chose the established solution—the patients’ right to consent. And emergency research ground to a halt ( [8] [9] [10] ).

The authors anchor their justification of acute care research to justice and beneficence. Concerning justice, Beauchamp and Childress ( [11] ) implied that there are two ways to think about justice: distributive justice and what is due to someone. Emergency patients are due the best treatment that scientific medicine can devise. Requiring informed consent from this population would be treating unequals as if they were equals. As Drs. McRae and Weijer ( [2] ) note, “many problems ... are unique to the emergency setting.”

Concerning beneficence, they say, “To appropriately protect participants in emergency research, we must think clearly about research risks.” They say that **minimal risk** requires “that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or physiologic examinations or tests.”

The Coalition Conference of Acute Resuscitation and Critical Care Researchers “proposed that ‘appropriate incremental risk’ become the threshold for acceptable risk in acute care research. Appropriate incremental risk means ‘the risks of research participation that exist relative to the consequences of the medical condition of such patients, or any potential risk of the experimental therapy relative to standard therapy’ ” ( [2] ).

In 1996, this definition of risk “effectively became part of new regulations issued by the DHHS and the Food and Drug Administration.”

Drs. McRae and Weijer ( [2] ) fear that “the literal interpretation” of the Coalition Conference’s definition and the new regulation “is that the more dire a patient’s illness or injury, the riskier the nontherapeutic procedures that may be performed on the patient. This is at odds with the intention of the Belmont Report’s principle of respect for persons’ requirement that vulnerable participants be protected in a way that is commensurate to their vulnerability.”

In analyzing research risk, the authors use “component analysis,” which the National Bioethics Advisory Commission has adopted. Component analysis recognizes different types of interventions (components) in clinical research—therapeutic and nontherapeutic. Presupposing equipoise, therapeutic research does not entail risk for the patient. Hence, risk occurs in nontherapeutic research. This understanding of risk will seem counterintuitive to those who think of risk as potential to be harmed. Thus, it may well require more debate, rather than resolve it. The authors justify research on this population by noting that a low level of risk occurs in everyday life.

In preferring **minimal risk** to appropriate incremental risk, the authors return to Weijer’s ( [12] ) understanding of **minimal risk** in the Belmont Report: “It is our contention that most acute care research could continue under a properly applied **minimal risk** threshold.” And with an eye to further research they conclude, “Empirical study should determine whether this is the case.”

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