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Consent for acute care research and the regulatory "gray zone"

Laura M. Beskow, MPH, PhD,
Center for Biomedical Ethics & Society, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Christopher J. Lindsell, PhD,
Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Todd W. Rice, MD, MSc
Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

In their article, "Partnering with Patients to Bridge Gaps in Consent for Acute Care Research" (Dickert 2020), Dickert and colleagues describe a vigorous and much-needed effort to improve informed consent for acute care research. In particular, their patient-centered approach is directly aligned with a frequent refrain: That the focus of informed consent should be on informing and protecting participants (rather than protecting institutions) and, in devising consent forms and processes, IRBs and investigators should strive to ascertain what would be important to prospective participants from the participants' perspectives (Institute of Medicine 2002).

Appropriate approaches to consent are one important component of the broader needs of this patient population for ethically designed and conducted research to identify effective interventions. This includes research to develop new drugs and procedures to treat acute illness and injury, as well as randomized trials to identify the best options among commonly used interventions for which practice varies and the evidence base is lacking.

For such research, it is essential to recognize that even the best-designed informed consent process cannot realistically achieve all the goals we might ideally hope for. Acute conditions often involve vulnerability and distress, so that patients' and perhaps even surrogates' capacity to consent may be limited. In addition, the window of time to initiate the intervention may be narrow, constraining both the chance to locate an appropriate surrogate if needed and to undertake a thorough consent process.

Finding ethical solutions to these realities is hampered by regulatory challenges. As Dickert and colleagues found, even attempts to simplify consent materials and organize them in patient-friendly ways can encounter resistance—despite containing all required elements—because "IRBs often request more comprehensive consent forms out of concern that regulatory entities may consider less detailed forms to be inadequate" (p.14).

In the U.S., alternatives to full prospective consent can only be considered for research that (among other criteria) involves no more than minimal risk to the participants (45 CFR 46.116(f)(3)). Controversies abound over how the concept of 'minimal risk' should be defined and operationalized. Examples include:

- Whether the level of research risk should be measured by comparison to the absolute standard of risks “ordinarily encountered in daily life or during the performance of routine physical or psychological examinations” (45 CFR 46.102(j)), versus measured as the incremental risk beyond those already faced by similarly situated patients (Westra et al. 2011);
- Whether mortality as a study endpoint is a de facto indicator of research risk (Silverman and Lemaire 2006); and
- Whether randomization between two “standard of care” interventions is itself a risk (Office of Human Research Protections 2014).

Resolving these kinds of controversies is vital, as the concept of ‘minimal risk’ is central to a regulatory “gray zone” that can halt otherwise beneficial research. Specifically, if randomized trials in acute settings—where the situation is not immediately life-threatening, but time to initiate the intervention and patients’ capacity to consent are significantly limited—are viewed as involving greater than minimal risk, they will neither qualify for waiver or alteration of consent nor meet criteria for what is known as “exception from informed consent” (EFIC).

In one real-life example, a proposed study of different oxygen saturation targets in mechanically ventilated adult patients sat squarely in this gray zone. Data suggested that usual care encompassed a wide range of oxygen management targets (Suzuki et al. 2013). Experts debated the potential for oxidative injury from higher targets versus ischemic injury from lower targets, and there was insufficient evidence to support either contention.

This was an ideal question to answer with a pragmatic comparative effectiveness trial. For such a study, allocation to an oxygen saturation target had to occur immediately upon initiation of mechanical ventilation, as this was likely the most important period in which to control oxygen exposure and improve outcomes. To achieve rapid allocation, the use of a cluster-randomized approach was optimal, such that different institutions would be randomized to different oxygen saturation targets. Thus, every patient at a given institution would be managed the same way, and that management would be known at the time mechanical ventilation was initiated. The distribution of oxygen targets across the entire population would be within the variability seen in usual practice but controlled in order to produce robust data concerning the clinical effects of different targets.

Some IRBs worried, however, that the proposed study involved greater than minimal risk. In general, IRB members may carry the same clinical biases about which level of oxygenation is best, despite the lack of evidence one way or the other. Others may simply see that the endpoints include harm (death or organ injury) and immediately declare that such a study involves more than minimal risk. A determination of greater than minimal risk does not allow for waiver or alteration of consent, but instead requires traditional written informed consent—likely from surrogates for the vast majority of patients in the study described here. This would almost certainly lead to accrual challenges and sampling bias because only patients who had a surrogate readily available or who were less severely ill so that they could provide meaningful informed consent for themselves would be enrolled. All other

patients would be systematically excluded, obfuscating the potential effects and biasing the results.

Further, because most patients who are mechanically ventilated are not at immediate risk of death, the proposed study failed to meet criteria for EFIC (Klein, Moore, and Biros 2018). Thus, if some IRBs were not comfortable making a minimal risk determination and the requirement to obtain full prospective consent could therefore be neither waived nor altered, and the proposed study was also not a candidate for EFIC, there was no viable mechanism to proceed under current U.S. human research regulations. Despite best efforts on all sides to find a resolution, the study was not undertaken due to regulatory ambiguity, and the question of which oxygen target is most beneficial for mechanically ventilated adult acute care patients remains unknown.

Dickert and colleagues' findings from robust stakeholder deliberation, informed by further empirical data that elucidates conceptions of risk, could help inform how we fill this regulatory gap. Evidence-based recommendations for ethically acceptable approaches to enrolling acute care patients in research, including delineation of the characteristics of clinical conditions and research designs that would allow for a minimal risk determination, would represent a tremendous advance. Key to this will be unequivocal emphasis on the full array of what makes clinical research ethical, including respect for potential and enrolled participants, the social and scientific value of the research question, scientific validity and methodologic rigor, favorable risk-benefit ratio, fair subject selection, and independent review (Emanuel, Wendler, and Grady 2000). Within this context, the door would be opened to developing patient- and family-facing materials and processes that, rather than being "disingenuous and disrespectful" (Dickert 2020)(p.14), could optimize realistic functions of informed consent (Dickert et al. 2017) while also recognizing its limitations.

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