

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Mary Beth Hamel, M.D., M.P.H., *Editor***Informed Consent, Comparative Effectiveness,
and Learning Health Care**

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Interest in learning health care systems and in comparative-effectiveness research (CER) is exploding. One major question is whether informed consent should always be required for randomized comparative-effectiveness studies, particularly studies conducted in a learning health care system. Our answer to this question is no. It will often be unethical to go forward with CER in which patients are randomly assigned to different interventions without their written, prospective, informed consent. However, in a mature learning health care system with ethically robust oversight policies and practices, some randomized CER studies may justifiably proceed with a streamlined consent process and others may not require patient consent at all.

The current oversight system, requiring informed consent for most clinical research, grew out of a scandal-ridden period in which people were included in research and exposed to considerable risk without their knowledge or consent. In intervening decades, the clinical-research enterprise has changed. Some research, including some CER, may pose only minimal risks, yet the potential effect on patients' welfare of answering the core question of CER — which standard interventions work best for whom — is immense.

Elsewhere we have presented an ethical justification for the transition to a learning health care system and for the streamlining of both consent requirements and oversight practices within the system.^{1,2} A key premise in our justification is that current consent and oversight practices too often overprotect patients from research that has little effect on what matters to patients, whereas in other cases oversight practices underprotect patients from medical errors and inappropriate medical management because they make research to reduce these problems unduly burdensome to conduct.

We also have put forward an ethics framework for learning health care to serve as the moral foundation for a learning health care system.² Our Common Purpose Framework builds on traditional principles of clinical and research ethics, including the Belmont Report, but is designed to provide guidance for activities in which research and practice are integrated to enable rapid, systematic learning. The Framework comprises seven moral obligations: first, respect the rights and dignity of patients; second, respect the clinical judgments of clinicians; third, provide optimal care to each patient; fourth, avoid imposing nonclinical risks and burdens on patients; fifth, reduce health inequalities among populations; sixth, conduct activities that foster learning from clinical care and clinical information; and seventh, contribute to the common purpose of improving the quality and value of clinical care and health care systems. The first six obligations fall on researchers, clinicians, health care administrators, institutions, payers, and insurers. The seventh falls on patients to participate in certain types of learning activities that will be integrated with their clinical care.

Extensive consultation with patients and other stakeholders is necessary for appropriate specification of the institutional implications of the Framework. All involved must appreciate that they are receiving care or working in an institution committed to the shared mission of continuous learning that feeds directly into improving patient care. An ethical learning health care system must have core commitments to engagement, transparency, and accountability in ways that are keenly sensitive to the rights and interests of patients. Patients will be engaged in two respects: by helping to set the CER priorities of the system and by serving on ethics-oversight panels that will review proposed CER studies in light of the obligations of the Common Purpose

Framework and other ethical requirements and determine the appropriate forms of consent and authorization.

In this system, all patients will be told that patients serve on ethics-oversight panels and how they operate. The panels will determine whether particular CER (and quality-improvement) activities fall above or below a threshold of negative effect on expected clinical outcomes or other outcomes or values that matter morally to patients. Research that falls below the threshold will be integrated into clinical care without specific notification to or consent from individual patients; however, public notification will be provided to the community of the system, including patients. Other CER studies, determined by panels to have minor but still meaningful effects on patients' interests, will proceed with specific notification to affected patients, who will have an option to decline participation. Still other studies, determined to be clearly above the threshold, will require prospective, written, informed consent before proceeding. The system will thus aim to counteract problems of both underprotection and overprotection.

Transparent mechanisms will ensure that patients and other stakeholders can easily learn which CER studies are ongoing. In addition, and critically, a learning health care system will be accountable for rapid modifications of clinical practice that are supported by CER findings and for providing public reasons when modifications are not made.

In learning health care systems with these ethically robust practices, it will be ethically acceptable for some randomized CER studies, having no or only minor effects on important patient interests, to proceed without informed consent from or specific notification to individual patients. Consider, for example, randomized studies that compare the effectiveness of sending medication reminders by text or e-mail to patients who have previously given permission to be contacted by either mechanism or the usefulness of repeating a routine laboratory test once or twice during a patient hospitalization when both are standard practice. In a mature learning health care system, an ethics-oversight panel might justifiably approve the integration of these studies into clinical care routines with only public notification to the community of the system that the research is being conducted.

Consider also a pragmatic, randomized clinical trial that compares two widely used hypertension medications, perhaps two diuretics, and in which there are no delineated clinical characteristics that would favor one drug over another for many patients. Although an algorithm identifies eligible patients, treating physicians make the final enrollment determination. Physicians and patients can override the randomized choice. Physicians may change drugs, adjust dosages, or add therapies for any patient at any time. This study is unlikely to negatively affect expected clinical outcomes for patients, and respect for physician judgment is maintained. The drugs are similar in administration and side-effect profiles, both drugs have acceptable side-effect profiles, and adverse events are rare. It is unlikely that patients would have personal preferences for one drug over the other. This trial therefore accords well with the obligations in the Common Purpose Framework requirements.³ In a mature learning health care system of the sort that we envision, simply telling patients about the study through a streamlined process and giving them an opportunity to decline participation would be an ethically acceptable, warranted mechanism of authorization. It may even be acceptable for an ethics-oversight panel to permit the study to proceed with broad notification to the community of the system, without requiring that individual patients be told about the randomization.

However, some randomized CER studies in learning health care systems cannot be ethically authorized by either of these mechanisms. Explicit informed consent will be required if risk, uncertainty, or informational need is higher. Included would be studies in which the prospect of differential clinical outcomes or considerable risk looms large as well as studies in which interventions are different in terms of other considerations that matter to patients. Consider a study that randomly assigns patients with back pain to acupuncture or to a home exercise regimen or that randomly assigns patients with scoliosis to surgery or to bracing. Even if the alternative treatments were considered standard practice and even if clinicians were uncertain and evidence was lacking about which is more effective, the two options have such different implications for patients' lives that informed consent is essential. Among the critical functions of hav-

ing substantial patient engagement in ethics oversight of CER (and other research) in learning health care is to ensure that patients' values, beyond their interest in securing the best possible clinical outcomes, are respected.

Our position that informed consent is not a morally necessary condition for the conduct of all randomized CER assumes a learning health care system grounded in a set of moral commitments against which specific studies have been vetted and found to satisfy the conditions that permit authorization through processes other than informed consent. The transformation to a learning health care system is still in its infancy, and no system on the path to this important goal has yet to adopt an ethical framework with accompanying policies and practices of the sort we are proposing. However, the Common Purpose Framework can provide helpful guidance in current health care settings. Some randomized CER studies that would assess favorably against the first four obligations of the Framework could proceed ethically with a streamlined consent process. These include studies that, in comparison with what patients would otherwise encounter in their care, have no expected negative effects on clinical outcomes or on other considerations that matter to patients.

Consider now the previously mentioned randomized clinical trial comparing two similar hypertension drugs to see what authorization approaches might be justified in the current environment. We suggested that in an ethically robust learning health care system, characterized by extensive patient engagement, transparency, and accountability, it would be ethically acceptable for the study to proceed with a streamlined consent process and potentially even without specific notification to affected patients. In the present context, in which morally relevant features of a mature learning health care system are not in place, proceeding without specific notification to patients would not be ethically acceptable. However, it may still be ethically justifiable to use a streamlined consent process, similar to that suggested by others,^{4,5} because the study has no apparent effects on the risks or burdens that patients otherwise face in clinical care (the third and fourth obligations), clinician judgment is respected (the second obligation), and the interventions do not differ on matters of importance to patients (the first obligation). In

the streamlined process, physicians would inform their patients about the study and the use of randomization. Their explanations would be brief, akin to the conversation that physicians typically have with patients about a new prescription, and accompanied by a short, written description. Patients would be given an opportunity to opt out of the research and to learn more if they wish, but patients would not be asked for written informed consent. This approach could be designed to be respectful of patients and less burdensome for them and for clinicians than the lengthier process entailed by current informed-consent requirements, thereby increasing the numbers of clinicians willing to take part and increasing the numbers of important clinical questions that can be addressed.

Clinical research varies widely in the risks to which patients are exposed and the degree to which research alters the care that patients receive in ways that matter to them. The importance of streamlining oversight and consent requirements, so that higher-risk research gets the focused attention it deserves and less consequential research can proceed more rapidly, is increasingly being acknowledged. As more low-risk CER is planned, it will be essential to identify additional, valid authorization mechanisms, rather than using a one-size-fits-all approach to informed consent. The transformation to ethically robust learning health care systems is critical to this goal.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. *Hastings Cent Rep* 2013;43:S4-S15.
2. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning healthcare system: a departure from traditional research ethics and clinical ethics. *Hastings Cent Rep* 2013;Spec No:S16-S27.
3. Faden R, Kass N, Whicher D, Stewart W, Tunis S. Ethics and informed consent for comparative effectiveness research with prospective electronic clinical data. *Med Care* 2013;51:Suppl 3:S53-S57.
4. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *N Engl J Med* 1999;340:804-7.
5. Morris MC, Nelson RM. Randomized, controlled trials as minimal risk: an ethical analysis. *Crit Care Med* 2007;35:940-4.

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