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.\(^3\) 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.
ethically robust practices, it will be ethically ac-

ceptable for some randomized CER studies, hav-
ing no or only minor effects on important patient
interests, to proceed without informed consent
from or specific notification to individual pa-
tients. Consider, for example, randomized stud-
ies that compare the effectiveness of sending
medication reminders by text or e-mail to pa-
tients who have previously given permission to
be contacted by either mechanism or the useful-
ness 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 sys-

tem that the research is being conducted.

Consider also a pragmatic, randomized clin-
ical trial that compares two widely used hyper-
tension medications, perhaps two diuretics, and
in which there are no delineated clinical charac-
teristics that would favor one drug over another
for many patients. Although an algorithm iden-
tifies 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 un-
likely that patients would have personal prefer-
ences for one drug over the other. This trial
therefore accords well with the obligations in
the Common Purpose Framework requirements. 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 par-
ticipation would be an ethically acceptable, war-
ranted mechanism of authorization. It may even
be acceptable for an ethics-oversight panel to
permit the study to proceed with broad notifica-
tion 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. Ex-
plicit informed consent will be required if risk,
uncertainty, or informational need is higher. In-
cluded would be studies in which the prospect
of differential clinical outcomes or considerable
risk looms large as well as studies in which in-
terventions are different in terms of other con-
siderations that matter to patients. Consider a
study that randomly assigns patients with back
pain to acupuncture or to a home exercise regi-
men or that randomly assigns patients with scoli-
osis to surgery or to bracing. Even if the alterna-
tive treatments were considered standard practice
and even if clinicians were uncertain and evi-
dence was lacking about which is more effec-
tive, the two options have such different impli-
cations 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, 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.

From the Berman Institute of Bioethics, Johns Hopkins University, Baltimore (R.R.F., N.E.K.); and the Kennedy Institute of Ethics, Georgetown University, Washington, DC (T.L.B.).


DOI: 10.1056/NEJMc1131674
Copyright © 2014 Massachusetts Medical Society.