VIEWPOINT

Ethics, Regulation, and Comparative Effectiveness Research
Time for a Change

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The US health care system is poised to learn more about preventing, diagnosing, and treating illness than has ever been possible. This change is powered by the increasing commitment to comparative effectiveness research, increases in practice-based research, and the increasing availability of data arising from electronic health information systems to help patients, clinicians, and others understand who benefits from which treatments. Much can be learned by observing the outcomes of the varied decisions that clinicians and hospitals make. However, for many health care questions, it is important to intervene by systematically varying care, for instance by randomly selecting the order in which a new practice is introduced into different parts of a system or by randomly assigning different commonly used treatments to patients who are good candidates for all of the approaches. Indeed, random assignment would be important to ascribe causality to the change.

These strategies to improve clinical care are hampered by regulations that, in areas such as this, no longer match current needs. A more fundamental problem is the entrenched view that research, including evaluation of treatments already approved and widely administered to patients, automatically creates higher risks than ordinary care. For example, a comparison study of marketed agents for routine bathing and decolonization of intensive care unit patients that randomized hospitals to one or another regimen required substantial review and evaluation by an institutional review board (IRB) to determine whether and how to obtain consent from patients, how to address the possibility that a prisoner might be admitted during the course of the study, and whether participating hospitals needed a preexisting relationship with one another.[1]

Another example involves significant debate about appropriate ethical oversight for a proposed study randomizing patients to morning or nighttime dosing of antihypertensive medications.[2] Clinical guidelines generally do not address timing of medication administration, although hypotheses exist for potential benefits of both nighttime and morning dosing. The study alters neither the medication prescribed nor the frequency of administration.

The so-called protections being debated reflect a view that informed consent is required for most activities labeled clinical research. This is true even of systematic investigations of aspects of patients' care that never are deliberated with or communicated to patients but instead are routinely decided at the level of the hospital or other administrative unit. This difference in norms discourages formal evaluation of routine care changes and becomes particularly striking when contrasted with hospitals' authority to change system-level care without any evaluation, transparency, or patient consultation—changing, for example, the ratio of nurses to patients and similar administrative decisions that could have profound effects on patient outcomes. The irony deepens when consent requirements become barriers to even low-risk studies intended to identify strategies to protect patients. An increasingly germane question for policy and for ethics is what level of oversight of comparative effectiveness studies is necessary.[3] Admittedly defining low-risk can be complicated and as patients become increasingly involved in their care, it will be important to solicit their views.

Recommendations Within Current Regulatory Regimens

Policies regulating clinical research should consider whether studies pose greater risks and burdens to patients than they would encounter in usual clinical care, both with respect to the intervention being studied and to patients' other interests, including the privacy, security, and confidentiality of health information. Addressing this issue will require revisions to current federal regulations, but in the shorter term, the following recommendations would be welcome.

Guidance

Some barriers to research in the name of ethical protection result from misinterpretations or overly restrictive interpretations of regulations. The Office for Human Research Protections, the Office for Civil Rights, and the US Food and Drug Administration should provide more complete and coordinated advice about permitted activities. Information about precedents—detailed real-life examples demonstrating acceptable ways to evaluate research protocols from both legal and ethical perspectives—would also be helpful. The National Institutes of Health Health Care Systems Research Collaboratory has provided examples.[4] Establishing and disseminating such precedents could help IRBs and privacy boards avoid unnecessarily restrictive decisions because of uncertainty about what regulations allow.

Redefine Health Care Operations

In any health system, systematic evaluation should be routine and continuous.[5] Existing rules recognize this by classifying quality improvement as operations. However, use of rigorous, systematic methods to improve health care quality often leads to classification as research, subject to the Common Rule and more strin-

gent research rules under the Health Insurance Portability and Accountability Act. Oversight of a broadened set of operations activities should be part of routine organizational processes other than IRBs and privacy boards, building on processes governing treatment and quality improvement, in cases for which such activity does not increase risks or burdens to patients.[6]

Incremental Risk-Based Approach

As described in federal proposals to modify regulations, more stringent oversight should focus on activities that increase clinical or privacy risks or burdens to patients.[7] Moreover, such risks and burdens should be examined in comparison with the risks of care patients would have experienced without the learning activity in place. All clinical care carries risk, and to assume that research automatically imposes additional risks beyond those the same patient would otherwise have experienced in clinical care may overinflate the risks of research and underestimate the risk of not conducting these evaluations.

New and Reformed Regulations

In the longer term, innovative health care systems will need a more holistic approach to oversight of both systems-level and individual-level interventions. Such oversight should be developed in consultation with patients, clinicians, researchers, and bioethicists. Indeed, patient participation in oversight is critical. Core to its principles will be transparency to all stakeholders about both the continuous learning to which the system is committed, about the ways in which data will be used for research and for all other purposes, and about the particular learning activities proposed.

Furthermore, one example of a broader oversight approach "rejects the assumption that clinical research and clinical practice are fundamentally different enterprises," and suggests that all stakeholders share a moral obligation to contribute to learning and improvement of care.[8] This ethical framework suggests that regulatory oversight should be refocused on specific features of learning activities rather than their motivation. Risk, both physical and informational, would be key, as would knowing whether an intervention involves treatments in common practice or the level of evidence for their use, whether the type of intervention is (or should be) typically discussed with patients, and whether analyses require new data collection. Such activities should be conducted with full transparency to patients, with commitments to share findings broadly. As an important aspect of this transparency, regardless of whether investigators are required to obtain formal informed consent from study participants, patients should be informed that their health information is being used for research, as well as for several other purposes.

Harmonized Regulation

Regulations of all Health and Human Services agencies should be harmonized to the greatest extent possible. New regulation should reward more robust engagement of patients in the research process, improve the degree to which uses of data beyond treatment are made transparent to the public, and broaden situations in which informed consent is not required or could be waived, including for systems-level evaluations of practices that health care institutions might otherwise introduce without any evaluation. Regulations should further specify circumstances under which waivers of consent, community consent, or streamlined consent procedures would be acceptable for randomized comparative effectiveness studies. Characteristics of such studies might be ones for which all interventions are in common use; eligibility is limited to patients who are good candidates for either approach; adverse effects, modality, and other features that might engage meaningful patient preferences or values are similar between compared approaches; and privacy risks are minimal. Regulations should not impose barriers to interorganizational collaboration or to widely disseminating important findings. Opportunities to improve outcomes through systematic evaluation of care are substantial. Research policies should enable this learning, not overprotect against it.

ARTICLE INFORMATION

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