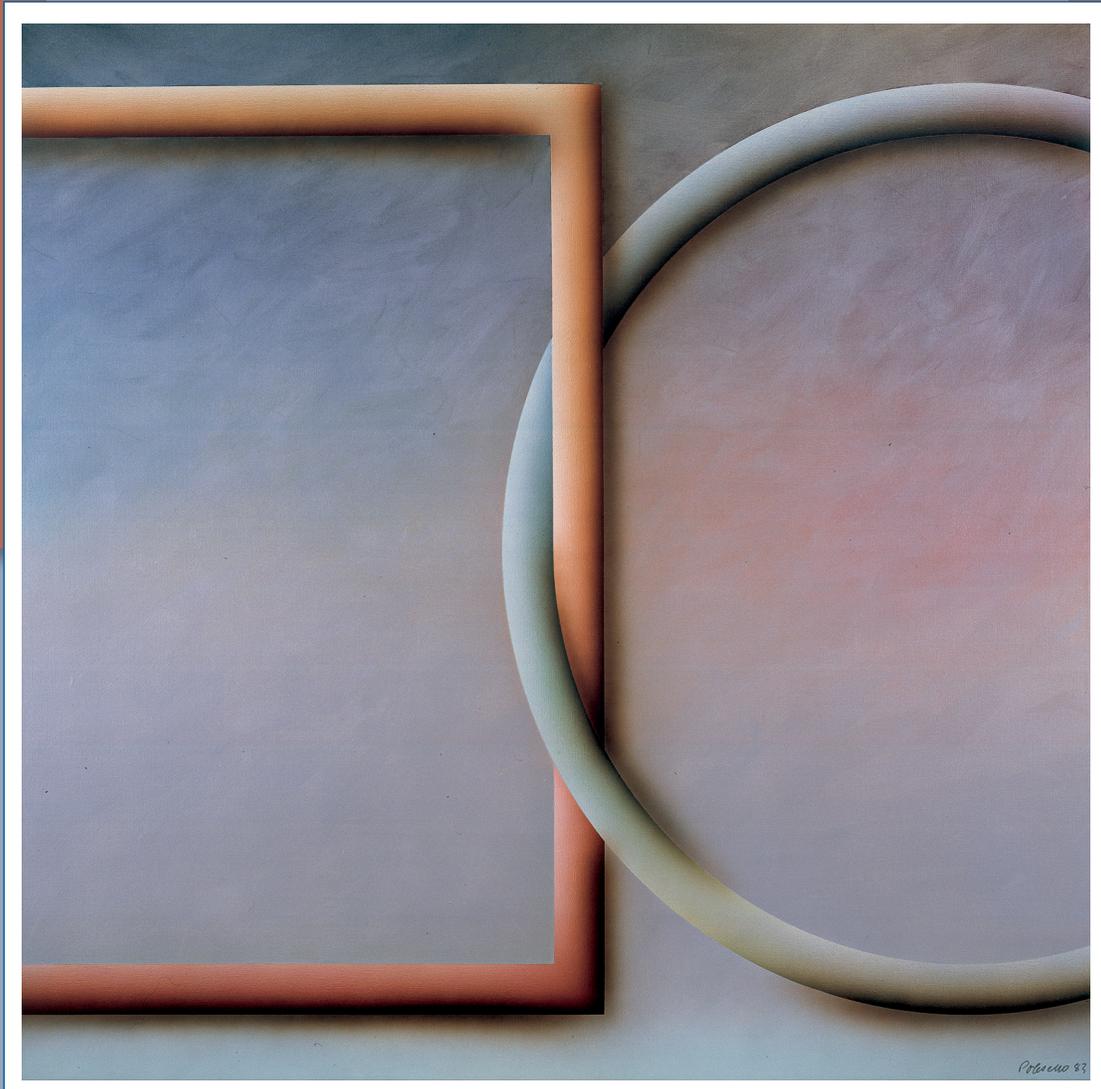


# ETHICAL OVERSIGHT



*of*  
**LEARNING HEALTH CARE  
SYSTEMS**

## AUTHORS

**TOM L. BEAUCHAMP** is a philosophy professor at Georgetown University and a senior research scholar at the Kennedy Institute of Ethics. He is the coauthor of *Principles of Biomedical Ethics*, which is in its seventh edition (Oxford, 2012), and he recently coedited the *Oxford Handbook of Business Ethics* (2011) and the *Oxford Handbook of Animal Ethics* (2011). Many of his articles were recently republished under the title, *Standing on Principles: Collected Works* (Oxford, 2010). Dr. Beauchamp's research interests are in the ethics of human subjects research and animal subjects research, the place of universal principles and rights in biomedical ethics, methods of bioethics, Hume and the history of modern philosophy, and business ethics.

**ANN C. BONHAM** is chief scientific officer at the American Association of Medical Colleges, where she directs the AAMC's array of programs that support all aspects of research and training. As the primary AAMC contact for external research organizations, Dr. Bonham addresses policy issues affecting research through engagement with key officials in the public and private sectors. Dr. Bonham also works closely with AAMC constituents to address their research needs, and represents the association on the national stage in forums dealing with research policy and administration and the research workforce.

**RUTH R. FADEN** is the Philip Franklin Wagley Professor of Biomedical Ethics and director of the Johns Hopkins Berman Institute of Bioethics. She is the coauthor (with Madison Powers) of *Social Justice: The Moral Foundations of Public Health and Health Policy* (Oxford, 2006), which defends a twin-aim theory of justice. Dr. Faden's current research focuses on questions of social and global justice and public policy, including national and global challenges in learning health care systems, health systems design and priority setting, and access to the benefits of global investments in biomedical research.

**STEVEN N. GOODMAN** is the associate dean for clinical and translational research at the Stanford University School of

Medicine. He is editor of *Clinical Trials* and senior statistical editor for the *Annals of Internal Medicine*. He recently cochaired (with Ruth Faden) an Institute of Medicine committee on the Ethical and Scientific Issues in Studying the Safety of Approved Drugs, and was appointed by the General Accounting Office to serve on the Methodology Committee of the Patient Centered Outcomes Research Institute. Dr. Goodman's research interests relate to the representation and measurement of evidence in medical research, determinants of the truth of medical findings, comparative effectiveness research, and the ethics of clinical research.

**CHRISTINE GRADY** is chief of the Department of Bioethics at the National Institutes of Health Clinical Center. She has coedited several books about the ethics of research, including, most recently, *Research Ethics Consultation: A Case Book* (Oxford, 2012) and the *Oxford Textbook of Clinical Research Ethics* (2008). Her research focuses on the ethics of clinical research especially consent, incentives, oversight, and international issues.

**CLAUDIA GROSSMANN** is a senior program officer with the Institute of Medicine's Roundtable on Value and Science-Driven Health Care. She currently leads the Roundtable's work in the areas of clinical effectiveness research and health information technology toward the realization of a learning health care system.

**STEVEN JOFFE** is a pediatric hematologist/oncologist at the Dana-Farber Cancer Institute, Children's Hospital Boston and Harvard Medical School. His research concerns challenges in human subjects research.

**NANCY E. KASS** is the Phoebe R. Berman Professor of Bioethics and Public Health in the Department of Health Policy and Management at Johns Hopkins Bloomberg School of Public Health and deputy director for public health in the Berman Institute of Bioethics. Her current research projects examine ethics for a learning health care system, including such topics as quality improvement and comparative effectiveness; informed consent in randomized trials; public health ethics, including surrounding issues of pandemic preparedness and obesity prevention; and ethics issues that arise in international health research.

**HARLAN M. KRUMHOLZ** is the Harold H. Hines, Jr., Professor of Medicine and director of the Robert Wood Johnson Clinical Scholars Program at Yale University School of Medicine, as well as director of the Yale-New Haven Hospital Center for Outcomes Research and Evaluation.

**JOEL KUPERSMITH** is the chief research and development officer of the Veterans' Health Administration, where he oversees the VA's extensive medical research program. He has over 160 publications—including two books—to his name and has most recently published on health policy issues, including comparative effectiveness research. As chief of the VA's research program, he initiated the Million Veteran

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### An HCR Special Report

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# Ethical Oversight of Research on Patient Care

BY MILDRED Z. SOLOMON AND ANN C. BONHAM

Health care in the United States is nearly twice as expensive as in other advanced countries, yet the quality of care is no better, and on many indicators it is worse, particularly for minority communities. There are problems of both over- and underutilization and an unacceptably high number of medical errors.<sup>1</sup> In recognition of these problems, the Institute of Medicine has called on health care leaders to transform their health systems into “learning health care systems,” capable of studying and continuously improving their practices.<sup>2</sup> Learning health care systems commit to carrying out numerous kinds of investigations, ranging from clinical effectiveness studies to quality improvement research and implementation science. Regardless of the kind of study, the common element is the collection of patient data, information about provider behaviors, patterns of care delivery, and administrative data about the patients and clinicians within one’s own system—all with the goal of building an evidence base to improve care.

There has been progress in realizing the IOM’s vision, but also many challenges. One of them has been lingering uncertainty about whether the data collection and monitoring central to learning health care systems is actually research and if so, what kind of ethical oversight it should have.

This is not a new question. The *Hastings Center Report* published a special report in 2006 on how best to oversee quality improvement research,<sup>3</sup> and in 2011, Emily Largent and her colleagues asked *Report* readers to imagine a health system that would expect its members to agree to being studied, with a series of structures and processes to ensure appropriate ethical oversight.<sup>4</sup> Yet so far, there has been no foundational analysis of the fit between the existing human subjects protection framework in use in the United States and the new kinds of data collection activities that are being, and increasingly will be, undertaken by learning health care systems.

Two companion feature articles in this volume, by a team at Johns Hopkins, fill this void. In the first, Nancy Kass, Ruth Faden, and their colleagues argue that the traditional distinction between treatment and research that has been the

bedrock of our human subjects protection framework for nearly four decades does not hold up in the changing landscape of a learning health care system, which by definition links treatment and research. Further, they argue that the existing framework is a serious impediment to undertaking the kinds of activities learning health care systems strive to carry out. The second feature article urges a new ethical foundation for determining the type and level of oversight needed. The authors assert that some activities that are clearly what many people might label “research” pose few risks or burdens and may not require consent, whereas some treatments pose substantial risks and should require more rigorous consent and oversight than is often the case. Therefore, they call for a new ethical framework, based on the level of risk and burden posed by any given data collection activity, not on whether an activity is likely to be seen as treatment or research.

Strikingly, one of the authors of these feature articles (Tom Beauchamp) was the principal architect of the *Belmont Report*.<sup>5</sup> Yet these papers call into question the research ethics framework the United States has relied upon since *Belmont* and publication of the Code of Federal Regulations, Title 45, Public Welfare, Part 46 (also known as the Common Rule), which governs human participation in research.<sup>6</sup>

The commentaries presented in this volume find both common cause with the Johns Hopkins’ authors and also offer important critiques. Christine Grady and David Wendler describe the Hopkins’ approach as “radical.” In particular, they caution that the Hopkins authors have postulated both too broad and too strong an obligation to conduct learning activities, which—if enacted in a manner consistent with how the obligation has been framed—would have “dramatic implications.” Emily Largent, Franklin Miller, and Steven Joffe agree with the importance of establishing learning health care systems and acknowledge that the current system may hamper some low-risk data collection activities. However, they believe that the research-treatment distinction is still useful and should not be abandoned. Jerry Menikoff, director of the Office for Human Research Protections, believes that the new ethical framework being offered by the Johns Hopkins team would require patient participation in interventional research trials and exempt too broad a swath of studies from the necessity of providing voluntary, informed consent.

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Joe Selby and Harlan Krumholz characterize three main kinds of studies likely to be undertaken in learning health care systems. They agree that oversight can be simplified for observational studies using existing clinical data without the imposition of additional data collection requirements beyond what is necessary for clinical care, but that oversight remains critical for prospective observational studies, which may require some additional data collection but where clinical decisions remain with clinicians and patients, and interventional studies, where treatment condition is assigned.

Writing separate commentaries from their respective vantage points within the Veterans Health Administration, Tom Puglisi and Joel Kupersmith offer lessons from the VHA experience. The VHA has been a leader in system-wide continuous quality improvement and has worked out an approach to ethical oversight of quality initiatives—what it calls “non-research health care operations”—that is different from the system in place for research oversight and does not require IRB review. This independent form of accountability has facilitated the conduct of quality assessments, program evaluations, and other forms of learning activities. Moreover, the VHA has been able to put this alternative method of oversight into place for quality initiatives, even as it abides by the Common Rule for activities it classifies as research.

Like the VHA, Richard Platt, Claudia Grossmann, and Harry Selker, who are members of the IOM’s Clinical Effectiveness Research Innovation Collaborative, propose a risk-based system of oversight that could proceed now, without changes to the Common Rule. They agree with the Faden team, and with VHA practice, that IRBs need not be involved and that consent is not necessary for a range of activities that do not confer more than minimal risk, such as the random allocation of hospitals or clinics to diverse but accepted care practices.

By inviting these commentaries, we aimed to provoke a national conversation about how to design ethical oversight that would adequately protect patients and clinicians without impeding the kinds of data collection activities essential to learning health care systems. Like the Johns Hopkins group, we believe there is not just an opportunity, but a moral imperative to mount clinical effectiveness studies, patient-centered outcomes research, quality improvement research, and implementation science. Transforming to learning health care systems is the ethical thing to do because systems that do not aim to study what they do and make improvements on the basis of what they learn inadvertently harm patients, maintain disparities, and waste resources.<sup>7</sup>

In short, our goal has been to stimulate more research on care both within health care systems and across them.<sup>8</sup> And we have reason for optimism. In February 2012, the two of us identified health care leaders from seventy academic medical centers whose chief executive and chief medical officers were committing financial and human resources to building the necessary infrastructure to become learning health care systems. We convened these leaders at an all-day meeting jointly sponsored by the Association of American Medical

Colleges and the IOM. Since then, the AAMC has continued to facilitate dialogue within and across most of these institutions through what has come to be called the Research on Care Community.<sup>9</sup> New transdisciplinary teams are bringing research methodologists together with physicians, nurses, economists, social scientists, decision scientists, and systems engineers to ensure that people with the right skills are in place to carry out a wide range of studies, capable of improving patient outcomes, eliminating health disparities, reducing medical error, and increasing the efficiency and value of health care services. If these efforts and ones like them emerging across the country are to be successful, and pending any changes to the Common Rule or forthcoming guidance, health care systems themselves will have to decide what kinds of ethical oversight are best. We hope the articles in this special supplement will help light the way.

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# The Research-Treatment Distinction: *A Problematic Approach for Determining Which Activities Should Have Ethical Oversight*

BY NANCY E. KASS, RUTH R. FADEN, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS,  
AND TOM L. BEAUCHAMP

For four decades the United States has had regulations to oversee research with human subjects. Early in this history, empirical research by Paul Appelbaum and colleagues resulted in a troubling finding: research subjects who are patients often blur the distinction between clinical research and treatment and view research activities as treatments best suited for their particular medical needs.<sup>1</sup> This blurring phenomenon, in which patients presume that research *is* treatment, was labeled the “therapeutic misconception.” Research ethics scholarship has considered strategies to minimize the therapeutic misconception and analyzed why and how clinical research is fundamentally different from clinical practice. For example, Robert Levine argued that the two need a clear-cut separation and that the notion of *therapeutic research* is illogical terminology.<sup>2</sup> In 2006, Franklin Miller also argued for sharp conceptual and moral boundaries between research and treatment:

Medical care has a personalized focus. It is directed to helping a particular person in need of expert medical attention. Clinical research essentially lacks this purpose of personalized help for particular individuals. . . . The distinctive purpose of clinical research [is] to develop generalizable knowledge.<sup>3</sup>

Drawing a sharp distinction between research and therapy can be appealing, but a growing number of activities in health care cannot be comfortably classified as either research or therapy, the one excluding the other. Participating in a clinical trial may be regarded by a woman with melanoma as her best “treatment option,” even if the specific treatment she receives is determined by random assignment. Quality improvement research designed to evaluate whether computer reminders of possible drug interactions might reduce medication errors does not alter the patient’s experience of clinical care, stands to improve clinical outcomes for future patients, and probably leads to better outcomes for the patients receiving care while the intervention is being tested. The recent and substantial federal investments in comparative effectiveness research,<sup>4</sup> practice-based research networks,<sup>5</sup> and large databases of aggregated health care claims<sup>6</sup> all support strategies to incorporate research questions into clinical settings and activities, generally with fewer constraints or burdens on both health professionals and patients than clinical research traditionally has imposed.<sup>7</sup>

The rise of quality improvement research and comparative effectiveness research in health care settings constitutes progress toward the goal of what the Institute of Medicine has called a “learning healthcare system,” in which we are “drawing research closer to clinical practice by building knowledge development and application into each stage of the healthcare delivery process.”<sup>8</sup> As clinical research and clinical practice move closer to a deliberately integrated system, the distinction between the two is increasingly blurred,<sup>9</sup> although the sharp distinction in U.S. regulations and research ethics literature

Nancy E. Kass, Ruth R. Faden, Steven N. Goodman, Peter Pronovost, Sean Tunis, and Tom L. Beauchamp, “The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight,” *Ethical Oversight of Learning Health Care Systems, Hastings Center Report Special Report* 43, no. 1 (2013): S4-S15. DOI: 10.1002/hast.133

## *Conceptual, moral, and empirical problems surround the received view that we can and should draw sharp distinctions between clinical research and clinical practice.*

remains in place. In the 1970s and for two decades thereafter, this distinction was helpful: for some forms of research, it sheds light on which activities require ethical oversight. Research that is closely integrated with health care—notably, health delivery research—was then uncommon, however. That is no longer the case, and regulations and research ethics need to change to accommodate the new landscape.

In this paper, we argue that conceptual, moral, and empirical problems surround the received view that we can and should draw sharp distinctions between clinical research and clinical practice. We start with the history of the research-practice distinction in the reports of a U.S. national commission and in U.S. federal regulations, and then offer a critical assessment of five characterizations of research that have been used in policy documents and the scholarly literature to try to make a sharp distinction between research and practice. We challenge the clarity and the tenability of these characterizations as a way of distinguishing research from practice.

As examples from both practice and research demonstrate, these five claims provide neither clear conceptual boundaries nor clear, morally relevant differences between clinical research and clinical practice. In our view, they have created practical moral problems for professionals in various fields in determining which health care activities are subject to third-party ethical oversight. The received view of the research-practice distinction leads to overprotection of the rights and interests of patients in some cases and to underprotection in others. We contend that a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients, and that provides oversight that, rather than being based on a distinction between research and practice, is commensurate with risk and burden in both realms.

### **Unethical Research Prompts U.S. Human Research Protections**

The first U.S. federal regulations governing research with human subjects appeared in 1974.<sup>10</sup> The National Research Act creating the National Commission for the Protection of Human Subjects was also passed in 1974 as a way of addressing public outcries regarding several human research studies that seemed harmful, exploitative, or unfair to vulnerable populations<sup>11</sup>—the most prominent of which was the Tuskegee Syphilis study. Although these studies had been

conducted by physicians on people who understood themselves to be patients, the studies were considered unambiguous instances of scientific research rather than clinical care, and they were almost uniformly viewed as unethical.<sup>12</sup> A public consensus emerged that research primarily serves the interests of science and of future patients rather than the interests of patients at hand, and that research is therefore prone, in ways clinical care is not, to exploit patients or expose them to unjustified harms. Traditional mechanisms for protecting the welfare of patients, such as reliance on professional integrity and the licensing of physicians, were widely judged insufficient to safeguard the rights and interests of patient-subjects.

The subsequent sweeping policy changes in the 1970s at the federal level required most human research to be overseen by a system that included review prior to the conduct of the research by an institutional review board charged with ensuring that research has a favorable benefit-risk balance, an adequate consent process, and a fair system of selecting subjects. Federal regulations thus came to demand impartial third-party oversight for research, but required nothing comparable for clinical practice (although the National Commission had judged, during the course of its deliberations, that innovative practice needed parallel oversight<sup>13</sup>). It was therefore essential, from a practical perspective, that “research” be defined in a way that could reliably identify which activities conducted in a clinical context with patients were subject to regulations and oversight, and which were not.

### **How Research Has Been Distinguished from Treatment**

Of the five characterizations of research that have been offered to make a sharp distinction between research and practice, two have been almost universally accepted as defining features, and the other three are widely held empirical assumptions or representations about how research is different from practice in morally relevant ways. The two defining features are that research (1) is designed to develop generalizable knowledge and (2) requires a systematic investigation.<sup>14</sup> The three empirical assumptions are that clinical research (1) presents less net clinical benefit and greater overall risk than does clinical practice, (2) introduces burdens or risks from activities that are not otherwise part of patients’ clinical management, and (3) uses protocols to dictate which therapeutic

or diagnostic interventions a patient receives.<sup>15</sup> We examine each.

### Research Is Designed to Develop Generalizable Knowledge

The one characteristic that is used nearly universally to define research and to distinguish it from practice is that research is designed with the objective of producing generalizable knowledge. The first published use of the term “generalizable knowledge” appears in the *Belmont Report*, which states that whereas practice “refers to interventions that are designed solely to enhance the well-being of an individual patient . . . and that have a reasonable expectation of success, . . . research designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.”<sup>16</sup>

In U.S. federal regulations, “research” is defined as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”<sup>17</sup> The Council for International Organizations of Medical Sciences (CIOMS) international ethics guidelines use similar language, adding some examples of generalizable knowledge that rely heavily on *Belmont*, namely, “theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference.”<sup>18</sup> The bioethics literature unvaryingly echoes the *Belmont* and regulatory claims that having an objective to produce generalizable knowledge is the central defining feature of research. Typical examples in this literature: “The overarching objective of clinical research is to develop generalizable knowledge,”<sup>19</sup> and, “this quest for generalizable knowledge in the service of improved health is what unites biomedical research.”<sup>20</sup>

Research is described in many policy documents and in the bioethics literature as an activity *designed*—or, alternatively, *intended*—to produce generalizable knowledge.<sup>21</sup> In this account, generalizable knowledge does not demarcate an activity as research if knowledge is obtained as an incidental finding or an unplanned by-product of clinical practice; rather, its production must be planned from the start.

As health care organizations move increasingly to become integrated systems of care and learning, the development of generalizable knowledge will be an explicit objective of these arrangements. Learning health care systems are by definition institutions designed and intended to *simultaneously* deliver the care patients need while capturing the experience of clinical practice in systematic ways that produce generalizable knowledge to improve care for both present and future patients. In such a system, the intent to produce generalizable knowledge will become an unreliable way of distinguishing research from practice. Here, the objective of delivering the

best possible clinical care for the patient at hand is integrated with the objective of learning in reliable, ongoing, and generalizable ways from real-world experience with patients.<sup>22</sup> For example, a system that ensures that critical measurements taken in the course of clinical care are made and recorded with high quality, with the intent that these measurements be used both to modify patient care as needed and also as part of cohort designs or other observational studies, is a system that is designing clinical care to simultaneously treat patients at hand and also to facilitate the production of generalizable knowledge.

One could always insist that the *research* involved in a learning health care system (for example, the aggregation and analysis of the measurement data for future purposes) is distinguishable from the *practice* involved (for example, the taking and recording of measurements for immediate patient care). But this objection misses the point. In a learning health care environment, practice is a continuous source of data for the production of generalizable knowledge, and the knowledge that is produced is used to continuously change and improve practice. Practice cannot be what it is, and cannot be of the highest quality that morally it must be, independent of its intimate connection to ongoing, systematic learning.

Even outside the context of a learning health care system, many activities have previously been designed to simultaneously contribute to generalizable knowledge and to produce the best clinical outcomes for patients. In an older vernacular, this activity was classified as *therapeutic research*.<sup>23</sup> One of the best examples, in our assessment, is pediatric oncology, which has more or less from its outset been so designed, in that an extremely high proportion of children with cancer are treated under multicenter research protocols. In fact, despite Levine’s influential claim that the term “therapeutic research” is illogical, in various areas of adult oncology and in other areas of medicine as well, many patients seek to receive their medical care through clinical trials that are designed to produce generalizable knowledge. In explaining the nature of the medical care and “treatment options” available in clinical trials, numerous Web sites at the Food and Drug Administration and the National Institutes of Health use language such as “treatment option,” “new treatment,” “new research treatments,” “treatment IND [investigational new drug],” “research treatments,” “new drug or treatment,” “new methods of . . . treatment of a disease,” “treatments for medical problems,” and the like.<sup>24</sup> For many patients who participate, clinical trials intended to produce generalizable knowledge are offered as treatment options that may present the best available treatment for their conditions.<sup>25</sup>

Another problem with the “generalizable knowledge” criterion, when used as a defining criterion, is that it assumes that producing generalizable knowledge is a binary function—that an activity either does or does not do this. As such, it does not acknowledge that there are different degrees of

## *Practice cannot be what it is, and cannot be of the highest quality that morally it must be, independent of its intimate connection to ongoing, systematic learning.*

generalizability. Sometimes, as is often the case with quality improvement research, generalizability does not extend beyond the health system being studied. It might even be limited to future patients of a particular physician or physician group, such as when ascertaining surgeon-specific success or complication rates. In other situations, the intent might be to generalize to all patients with a given condition treated anywhere.

Some might argue that we have not shown that generalizable knowledge does not distinguish research from practice, and that our examples show only that research can occur in conjunction with practice—a claim that has never been in doubt. But consider further the example of pediatric oncology, in which virtually all patients are enrolled in clinical trials and enrollment in the trial is considered to be a standard of care. The practice context is constructed to bring the most pertinent forms of scientific understanding to bear on clinical care, and clinical care generates new scientific learning. Generating and using generalizable knowledge can thus be a deliberate and integrated aspect or part of practice, not a set of maneuvers logically distinct from it. Research therefore cannot be distinguished from practice by appeal to the criterion of generalizable knowledge.

Our arguments do not diminish the importance and value of the concept of activities that yield generalizable knowledge in medical science. We merely reject the claim that generalizable knowledge is uniformly serviceable as the primary criterion to differentiate clinical research and clinical practice. We do not say that research and practice can *never* be distinguished by appeal to the criterion of generalizable knowledge. In many forms of clinical research, they can. But in an environment comparable to a learning health care system, which we expect to become an increasingly important form of medical practice, production of knowledge generalizable at some level beyond the patient at hand will become an essential part of the routine practice of medicine—just as it has been for decades in pediatric oncology. In such a context, it cannot be a defining condition to distinguish research from practice.

### **Research Requires a Systematic Investigation**

Most policy and guidance documents for research oversight or research ethics characterize research as being in some respect systematic. The U.S. Code of Federal Regulations, for example, states that one condition of the

definition of “research” is that it is “a systematic investigation, including research development, testing and evaluation.”<sup>26</sup> While the systematic collection of data according to a pre-defined method may be important to the production of generalizable knowledge in the biomedical context, this feature cannot serve to distinguish research from a large body of clinical practice today. The systematic collection of data is ubiquitous in contemporary clinical medicine. In many health care contexts, the systematic collection of data is now viewed as good clinical practice and even as obligatory. Hospitals must systematically collect data on a variety of health care services and outcomes in order to be accredited in the United States.<sup>27</sup>

Most U.S. hospitals are part of the Centers for Medicare and Medicaid Services’ (CMS) Hospital Inpatient Quality Reporting program,<sup>28</sup> which requires data to be collected on numerous outcomes to determine if a hospital meets quality benchmarks.

Data about performance on these and other outcomes are often made public and can be used by researchers, influencing private and public sector decisions about health care purchasing and rates of provider reimbursement. Virtually all major insurance companies have purchased or established organizations that systematically collect and analyze the administrative data generated through health claims that are used for a variety of purposes, including quality improvement, provider performance measurement, and safety surveillance, as well as being sold to life sciences companies to assist in their postapproval research and marketing needs.<sup>29</sup>

The number of hospitals in the United States with electronic medical record systems is growing, although currently only a small portion can use their information technology systems for the “meaningful uses” of improving “quality, efficiency, or safety” for their own patients.<sup>30</sup> Nonetheless, several large health care systems in the United States have implemented programs that continuously collect data on clinical services and outcomes to improve the quality of care delivered to their own patients. Intermountain Healthcare, for example, encourages its clinicians to identify ideas for clinical improvement, creates internal protocols, and tracks outcomes, using a computerized system, to continuously improve treatment guidelines for its patients.<sup>31</sup> The Veterans Health Information Systems and Technology Architecture (VistA) is a second example. VistA is described as “an integrated inpatient and outpatient electronic health record for VA patients, and administrative tools to help VA deliver the best quality medical

care to Veterans.<sup>32</sup> VistA systematically collects data in and about ongoing clinical practice to simultaneously improve clinical services and facilitate the production of knowledge to be used more broadly.<sup>33</sup> Another example are Practice-Based Research Networks (PBRNs), which are groups of primary care clinicians and practices that, with federal funding, jointly create infrastructure for systematic investigation of questions related to community-based practice and to improve the quality of care in these centers. This system to collect data is designed not only to integrate research into practice but also to improve the quality of the care delivered.<sup>34</sup>

In each of these three examples, it is futile to try to distinguish a research activity from a practice activity by showing that it relies on the systematic collection of data. The language of “systematic investigation” is of no help unless increased weight is given to the concept of an “investigation”—which may simply be another word for “research,” in which case the definitions are viciously circular. The production of generalizable knowledge and the systematic collection of data were helpful in distinguishing research from practice when the delivery of health care was largely treated as a given practitioner’s art, patients’ health information was not easily aggregated or disseminated, and regulators did not require data to be collected on a routine basis. But in the current environment, the science of health care delivery is required to deliver high quality care, and regulators and payers also regularly require the systematic collection of data. Accordingly, the use of features such as systematic investigation to distinguish research from practice is of decreasing value.

### Research Presents Less Net Clinical Benefit and Greater Overall Risk

We now turn from the two commonly accepted conceptual conditions of “research” to three empirical assumptions often presented to identify morally relevant distinctions between research and practice (or treatment). The first of these is that research, in contrast to clinical practice, offers patients both less prospect of net clinical benefit and more overall risk. The underlying moral thesis is that research with patients requires special oversight because it is less likely than clinical practice to be in the patient’s best clinical interests and more likely to impose significant clinical risk. But is this empirical thesis defensible?

Among research ethics policy documents, the *Belmont Report* was the first to provide definitions to distinguish practice from research, and it speaks directly to this empirical assumption. The National Commission stated that to qualify as *practice*, the following conditions must be satisfied: (1) the purpose of an intervention is to provide diagnosis, preventive treatment, or therapy; (2) the intervention is designed solely to enhance the well-being of an individual patient; and (3) the intervention must have a reasonable expectation of

success.<sup>35</sup> That interventions used in practice are expected to have a reasonable prospect of success is reinforced in the Food and Drug Administration’s position that the basic criteria for drug approval—thereby moving a drug from research to practice—is that “the drug is safe and effective in its proposed use(s), and the benefits of the drug outweigh the risks.”<sup>36</sup> By contrast, OHRP guidance states that some kinds of research with patients use “an untested clinical intervention.”<sup>37</sup> The implication is that in research in which clinical interventions are being evaluated, the threshold of a reasonable expectation of success, in which the prospect for benefit outweighs the prospect for risk of harm, has not yet been crossed.

So ingrained is the view that research with patients is riskier and less likely to produce net clinical benefit than clinical practice that some have used this empirical assumption to argue that quality improvement studies are not research. For example, R.P. Newhouse and colleagues maintain that “in QI [quality improvement], the objective is to benefit those patients who are served. In research, the subjects put themselves at risk of harm knowing in advance that personal benefit may not result,” whereas the patients in a clinical unit affected by a quality improvement program do not.<sup>38</sup> Mary Ann Baily, explaining why a particular activity should be classified as quality improvement rather than as research, argues that it “was not designed . . . to test a new, possibly risky method.”<sup>39</sup>

Others have challenged the empirical assumptions that participation in research carries considerable risk, that it is riskier to patients than receiving care outside of research, and that patients in clinical research have poorer outcomes or have a lower likelihood of net clinical benefit than patients not in research. Although empirical evidence is limited, several systematic reviews have concluded that patients in clinical trials fare no worse clinically than do patients in clinical practice.<sup>40</sup>

These findings make sense. Interventions—whether new or established—that come to be tested in clinical trials are a small fraction of those ultimately used in clinical care. There is growing recognition that many therapies, tests, and interventions administered regularly in clinical practice are of unproven value, and that many may actually be harmful; a significant percentage of clinical procedures would not satisfy the *Belmont* condition that practice entails a reasonable expectation of success. The Institute of Medicine now estimates that more than half of treatments in current use lack adequate evidence of effectiveness,<sup>41</sup> and many surgical and diagnostic procedures diffuse into practice with little or no prior scientific study.<sup>42</sup> Mounting evidence indicates that patients in ordinary clinical care are often at risk of receiving suboptimal outcomes and of being harmed, however inadvertently, as a consequence of inadequate evidence, unproven traditional practices, and biases in clinical judgment.<sup>43</sup>

Celebrated examples exist of therapies whose adoption was widespread but that later were shown to be useless or harmful. These include gastric freezing,<sup>44</sup> carotid bypass surgery,<sup>45</sup>

*There is no good evidence to support the empirical assumption that research studies, as a class, are more likely than clinical practice to run counter to the medical best interests of patients.*

antiarrhythmic drugs for sudden death,<sup>46</sup> high-dose chemotherapy followed by bone marrow transplantation for breast cancer, bone cement for treatment of osteoporotic spinal fractures,<sup>47</sup> lung-volume reduction surgery,<sup>48</sup> and postmenopausal estrogen.<sup>49</sup> Before these interventions were generally discredited, many clinicians believed it was unethical to withhold them from patients. In the breast cancer case in particular, suggestive results from perceptible initial improvement using aggressive applications in early-phase trials led to requests for increased access from many patients for use of this unapproved product. Approximately forty thousand women were given access—despite weak evidence of efficacy—while only one thousand women participated in the clinical trial. The completed clinical trial established that this investigational strategy provided no benefits over standard therapies and was in fact associated with substantial morbidity.<sup>50</sup>

Even for drugs and devices that have secured FDA approval, there can be limited evidence on how well the drugs work in multiple populations with whom drugs were never systematically evaluated. Patients who join randomized, controlled trials “differ significantly from those in the general population with a given disorder in terms of age, sex, race, severity of disease, educational status, social class, and place of residence.”<sup>51</sup> Also, “women, children, the elderly, and those with common medical conditions are frequently excluded from RCTs [randomized, controlled trials],”<sup>52</sup> again underscoring that medications are commonly provided in clinical practice to many populations or in settings in which studies never were conducted. A similar situation is the off-label use of approved medications, where little evidence underlies the use of fairly potent drugs or devices in untested contexts.<sup>53</sup>

Substantial evidence now points to the frequency and severity of the clinical harms that patients experience as a consequence of the medical errors and lack of supervision that occur in clinical care. The exact number of patients harmed from health care is unknown, but we know that approximately 100,000 people die annually in the United States from health care-acquired infections,<sup>54</sup> approximately 100,000 die from health care-related venothromboembolism,<sup>55</sup> and scores of thousands die from care that results from teamwork failures, medication errors, falls, diagnostic errors, decubitus ulcers, medical device errors, or treatment that otherwise does not conform to evidence-based best practices.<sup>56</sup> We do not know how much of this harm can be averted, but where focused improvement efforts have been adopted, most of the harms turn out to be preventable.<sup>57</sup>

These problems in medical practice can be constructively compared to the risks and the benefits of comparative effectiveness research, which is often directed at ascertaining which of two or more widely used interventions for the same indication works best for which patients. In these trials, the clinical benefit experienced by the patient-subjects is little different from that in ordinary clinical care, since both interventions under study are accepted clinical options—neither experimental nor investigational. All participants receive a therapy that conforms to *Belmont’s* “reasonable expectation of success.” Other clinical research studies evaluate strategies designed to prevent medical error—for example, by evaluating the effectiveness of computer reminders for physicians or of checklists for surgeons—but these studies are overlaid on whatever usual, presumably net beneficial, care patients already receive, and probably stand to reduce the harms to the patients whose care is the focus of the research experience, rather than to increase them.

None of this is to deny that some research studies expose patients to risks of harm. Of course they do. But so does standard care. The point is that there is no good evidence to support the empirical assumption that research studies, as a class, are more likely than clinical practice to run counter to the medical best interests of patients, and a fair amount of research suggests that they may serve their medical interests better.

### **Research Introduces Clinically Irrelevant Burdens and Risks**

The second empirical assumption invoked to identify a morally relevant distinction between research and practice is that research with patients often introduces risks, burdens, or inconveniences that are unrelated to patients’ clinical care needs (and that no comparable clinically irrelevant risks or burdens are imposed in clinical care outside of research). Jerry Menikoff, for example, maintains that “doing research involves intentionally exposing persons to risks, and not for the primary purpose of treating them or making them better but rather to answer a research question. . . . doing research is often going to involve some level of risk to research subjects, risk that is being imposed for a purpose other than for their benefit.”<sup>58</sup> Arthur Schafer makes a distinction between the normal risks of practice and the “added hazards, discomforts, or inconveniences” of research while maintaining that in re-

search, “procedures may be undertaken that are not strictly necessary for the treatment or cure of a particular patient.”<sup>59</sup>

Some clinical research—but not all—imposes risks and burdens on patients beyond those necessary for sound clinical management. More pertinent to our concerns is the linked empirical assumption that clinical care, by comparison, does not impose extraneous risks or burdens on patients beyond those associated with sound clinical management. Evidence suggests, to the contrary, that even routine clinical care often includes tests, visits, and medicines where no evidence of clinical improvement or relevance exists and where interventions carry significant risks or burdens.<sup>60</sup> These tests and visits may be poorly coordinated, requiring patients to make numerous trips to obtain a diagnosis or undergo a procedure, and sometimes to repeat the same tests. That these interventions are intended to help the patient does not diminish the fact that additional risks and burdens unnecessary for sound clinical management are introduced. Various studies and reviews have documented that a range of forms of the overutilization of medical services exposes patients to burdens and risks without conferring a reasonable prospect of offsetting clinical benefits.<sup>61</sup>

Risks to privacy and confidentiality are also found in practice settings, not merely in those of research. Although little data exist on the frequency and seriousness of breaches of confidentiality in personal medical records, the media has provided numerous reports of lapses in data privacy practices, some of which were of significant magnitude, and some of which also resulted in unauthorized disclosures of patients’ private medical information.<sup>62</sup> Many stakeholders—including physicians, health insurance companies, pharmacists, local hospitals, state bureaus of vital statistics, accrediting organizations, employers, life insurance companies, medical information bureaus, and attorneys—can gain access, for various purposes, to identifiable information from patients’ medical records.<sup>63</sup> Some of these individuals and groups do not examine the medical record solely to advance the patient’s clinical management. It remains unclear that evidence exists regarding which enterprise—clinical practice or clinical research—imposes the higher level of burdens and risks on patients beyond those associated with sound clinical management.

### **Research Protocols Dictate Which Interventions a Patient Receives**

The third empirical assumption used in the literature to identify a morally relevant distinction between research and practice is that in clinical research, unlike clinical practice, a patient’s clinical management is often determined by a preestablished protocol. Different authors have described the ethical import of this distinction between research and practice in different ways. According to Laura Tapp and col-

leagues, assigning treatment by protocol entails that patient care becomes less individualized, that flexibility to use other medicines may be reduced, and that patients’ needs may not be put first.<sup>64</sup> Steven Grunberg and William T. Cefalu state that in clinical research, “the selection of certain aspects of the treatment regimen is taken out of the hands of the treating physician,”<sup>65</sup> and Michael Kottow argues that “when treatment decisions are made by protocol, the patient becomes ‘a therapeutic orphan.’”<sup>66</sup>

Some clinical research undeniably uses an algorithm to determine which intervention a patient-subject receives. In the classic randomized clinical trial, interventions are assigned to subjects randomly. But because there is often disagreement and wide practice variation within the clinical community for the kinds of interventions tested in these trials, which intervention any given patient will receive in standard practice can be determined more by geographic location or hospital catchment area, or by which surgeon they see, than by their individual health characteristics.<sup>67</sup> This contingency introduces an element of chance in the way treatment choices are made in ordinary clinical practice that often goes unacknowledged.

External constraints on care patients receive in ordinary practice are also increasing.<sup>68</sup> Formularies restrict which pharmaceuticals can be prescribed (or reimbursed), often assigning patients to generic or less expensive “first-line” medications.<sup>69</sup> Certain diagnostic tests that patients may seek or that physicians may want to order are not allowed under reimbursement policies that direct and restrict which treatments or tests can be employed for which patients or symptoms. Hospital management sometimes creates standardized care protocols and policies regarding various aspects of care. Most hospitals, for example, are allowed to substitute lower-cost medicines when physicians have ordered a more expensive one.<sup>70</sup> Reimbursement policies often restrict the circumstances or number of times when tests such as mammograms or eye exams can be obtained, or they deny coverage altogether for certain tests and procedures.<sup>71</sup> Gatekeeping strategies, requiring prior authorization or second opinions, also constrain patient or physician choice in clinical care in favor of a broader goal of improved clinical effectiveness or cost-effectiveness in the aggregate.<sup>72</sup>

At the same time, efforts are under way in clinical research to design studies that can accommodate patient or physician preferences, both to increase the transportability of research findings to clinical practice and to make it easier to conduct research in nonacademic clinical settings. This goal is also present in the design of clinical trials, where the available treatment options can be wider than those in standard practice. The Clinical Antipsychotic Trials of Intervention Effectiveness, for example, randomly assigned patients with schizophrenia to one of six FDA-approved, widely used therapies, all of which have demonstrated evidence of clinical benefit. Participants could switch to another therapy at any

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time, without having to withdraw from the trial, based on a clinician's or patient's view that the drug is not working, that the drug is not tolerable, or that another drug would be better.<sup>73</sup> Similarly, in the Spine Patient Outcome Research Trial Study, which examined the role of surgery in back pain, patients assigned to nonsurgical therapy could choose to receive surgery if they felt it was necessary, and 17 percent did. Among those who continued with nonsurgical therapy, almost any modality was allowed.<sup>74</sup>

We are not claiming that clinical management is as tightly controlled in all practice settings as it is in some clinical research protocols. Our claim is that the control over therapeutic options in research and clinical care contexts is often not so widely different as some have portrayed it and that “personalization” of therapy is neither a given in clinical care (even though there is often an illusion of such) nor unobtainable in clinical trials.

### **Practical and Moral Problems for Ethical Oversight**

**W**e have argued that the conceptual cornerstone of how research is defined in policy documents and the ethics literature—namely, as a systematic investigation designed to produce generalizable knowledge—is becoming an increasingly problematic way of distinguishing research in clinical practice contexts from health care or practice activities. We have also argued that three reasons that have often been offered for why research (but not clinical care) is morally problematic—such that it must undergo formal oversight and prior review—all rest on empirical assumptions that are questionable at best.

Relying on this faulty research-practice distinction as the criterion that triggers ethical oversight has resulted in two major problems. The first is what we might call a practical problem and has received considerable attention in recent years. We have seen delays, confusion, and frustrations in the regulatory environment when IRBs labor to interpret proper guidance in activities that increasingly challenge these boundaries. This practical problem has sometimes risen to the level of a federal investigation because thoughtful and experienced professionals have interpreted regulatory guidance differently

or cannot determine whether some body of procedures constitutes research or practice.<sup>75</sup>

The second, less-discussed problem is that relying on the flawed research-practice distinction as the basis for prior review and oversight has resulted in a morally questionable public policy in which many patients are either underprotected from clinical practice risks (when exposed to interventions of unproven effectiveness or to risks of medical error) or overprotected from learning activities that are of low risk from the standpoint of patients' rights and interests and that stand to contribute to improving health care safety, effectiveness, and value.<sup>76</sup>

Unlike the research context, no third-party oversight is currently required to ensure ethical use of interventions of unproven clinical benefit and unknown risk in clinical practice. There is no prospective moral scrutiny of practice comparable to the scrutiny of research, even though practice contexts can put patients at unjustifiable risk, leaving them deeply underprotected. For example, patients may have surgery at the hands of surgeons or teams who rarely perform such an operation, despite empirical evidence that low-volume hospitals have worse outcomes than high-volume hospitals.<sup>77</sup> In many respects, these patients are experimental subjects, often without their knowledge or consent, with the indefensible difference being that their experience will not inform the treatment of others.

Such underprotection is one side of the problem; overprotection is the other side. We are not aware of empirical data that quantify annually the numbers of low-risk observational studies and other research projects that do not alter patients' clinical experience or increase their medical risks, or the numbers of patients who are included in such studies, but the numbers are likely to be significant. Requiring that all activities that are designed to produce generalizable knowledge and that collect data systematically must undergo prior review by an ethics committee, even when patients' clinical care is in no respect changed, is a misplaced moral criterion of what needs review and is a deep weakness in our current system. Recent proposed changes to federal regulations justifiably suggest significantly streamlining, if not eliminating altogether, prior ethical review of some research of this sort.<sup>78</sup>

Overprotection is not simply a nuisance. The required oversight is costly in terms of time, human energy, and money.<sup>79</sup> It also results in an overburdened IRB system whose ability to provide quality oversight in situations where it is most needed is likely compromised.<sup>80</sup> Moreover, addressing the overprotection problem will itself facilitate the conduct of exactly the type of learning needed to decrease the problem of underprotection in clinical care. An investment of resources to ensure both the safety of patients and public trust in our learning activities is critically important and morally justified when merited by the risks and burdens to which patients might be exposed, rather than protections being based on a less justifiable practice-research distinction.

Requiring only what is classified as research to undergo the burdens and costs of extensive oversight—on the thin grounds on which we have commented—creates the situation that we are now in: the policy creates disincentives to rigorous learning, thereby increasing the likelihood that interventions will continue to be introduced into clinical practice and health care systems in the absence of scientific efforts to evaluate their effects.<sup>81</sup> Given the risks of harm that can and do occur in practice, an oversight system that stalls exactly the type of learning that could reduce the serious risks of clinical care needs reconsideration. We believe it is possible to design such a system, while still allowing the substantial and necessary room for the exercise of physician autonomy and judgment.

### Rethinking What Matters Morally

The traditional definitions and descriptions of clinical research and clinical practice are becoming blurred as a model of health care emerges in which practice and learning are integrated, where a central goal of the health care system is to collect, aggregate, analyze, and learn from patient-level data, and where clinicians are expected to make evidence-based practice decisions guided by the general knowledge produced from structured learning. This emerging way of organizing health care did not prevail when federal regulations governing research involving human subjects were initially developed, but it increasingly does today.

Today's heightened interest in comparative effectiveness, integrated learning health care systems, and continuous quality improvement provides an opportunity to rethink what matters morally in protecting the rights and interests of patients. Our current regulatory system has served us well in critical respects, and conscientious investigators have appreciated the importance of ethical review of their activities. However, our system of oversight relies too heavily on the research-practice distinction to identify which activities warrant ethical review and to determine when patients are at risk and in need of oversight protection. We need to identify more efficiently which interventions work, how errors can be

reduced, and when interventions or tests should be administered or avoided for groups of patients. The labels “research” and “practice” are poor proxies for what should be our central moral concerns, and they no longer serve the purpose they did three or four decades ago. It is time to create a more balanced and relevant understanding of what matters morally as American health care begins to transform to a system in which learning and clinical practice are deliberately and appropriately integrated.

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# An Ethics Framework for a Learning Health Care System: *A Departure from Traditional Research Ethics and Clinical Ethics*

BY RUTH R. FADEN, NANCY E. KASS, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS, AND TOM L. BEAUCHAMP

Calls are increasing for American health care to be organized as a learning health care system,<sup>1</sup> defined by the Institute of Medicine as a health care system “in which knowledge generation is so embedded into the core of the practice of medicine that it is a natural outgrowth and product of the healthcare delivery process and leads to continual improvement in care.”<sup>2</sup> We applaud this conception, and in this paper, we put forward a new ethics framework for it. No such framework has previously been articulated. The goals of our framework are twofold: to support the transformation to a learning health care system and to help ensure that learning activities carried out within such a system are conducted in an ethically acceptable fashion.

A moral framework for a learning health care system will depart in important respects from contemporary conceptions of clinical and research ethics. The dominant paradigm in research ethics and in federal regulations has relied on a sharp distinction between research and practice—a segregation model that dates to the influential publications of the National Commission for the Protection of Human Subjects in the 1970s.<sup>3</sup> The learning health care system, by contrast, proposes that it is acceptable and indeed essential to integrate research and practice.<sup>4</sup> From this perspective, the dominant ethical paradigm from the 1970s to the present time is anti-

thetical to and problematic for the learning health care system, at a time when clinical practice is far from optimal and learning to improve care is sorely needed. Several hundred thousand people die needlessly each year from medical mistakes.<sup>5</sup> There is reason to believe that adult patients receive only approximately 50 percent of recommended therapies,<sup>6</sup> and that up to 30 percent of health care spending is wasted.<sup>7</sup> The need to improve health care is urgent, yet the current ethics paradigm may hinder improvement. For example, the expansion of one of the most successful quality improvement interventions ever—saving thousands of lives by preventing central line-associated bloodstream infections in intensive care units—was almost halted due to concerns about research ethics oversight.<sup>8</sup> But few have come forward to express concerns and oversight for the thirty thousand or so people who will die unnecessarily each year in the United States from this type of infection.

Quality improvement and comparative effectiveness research are emblematic of the kinds of ongoing learning activities that a learning health care system is designed to promote. As we argue in the first article in this supplement to the *Hastings Center Report*, quality improvement and comparative effectiveness research bring into sharp relief the problems with the criteria traditionally used to distinguish research and practice. The fuzziness of the distinction, coupled with the oversight burdens that are required of research but not of practice, creates dubious incentives to redesign quality improvement and comparative effectiveness activities in ways that minimize the likelihood that they will be classified as re-

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# *Securing just health care requires a constantly updated body of evidence about the effectiveness and value of health care interventions and of alternative ways to deliver and finance health care.*

search, even at the cost of their rigor, utility, dissemination, or value.<sup>9</sup> There have been recent attempts to modify the dominant paradigm to accommodate at least some kinds of quality improvement and comparative effectiveness research,<sup>10</sup> but these efforts are limited in reach and impact. Going forward, the fundamental structure and assumptions of the traditional segregation model rest too heavily on an unjustifiably sharp distinction between research and practice. The traditional model now stands to frustrate integrated, real-time learning, which is at the heart of where our health care system should be headed.

The framework we propose in this paper rejects the assumption that clinical research and clinical practice are, from an ethics standpoint, fundamentally different enterprises. It departs significantly from today's research ethics and clinical ethics paradigms in two key respects. First, the framework sets a moral priority on learning. It includes a specific, novel obligation on health professionals and health care institutions to be active contributors to learning in health care. We argue that a similar obligation extends to patients, who have traditionally not been conceived in research ethics as having a duty to contribute to the ongoing learning that is integrated with the health care they receive. Second, the framework includes an obligation to address problems of unjust inequalities in health care—an obligation that reaches beyond the demands of justice in traditional and contemporary codes of research and clinical ethics. Our view is that the time has come for these changes to be recognized as central moral obligations in health care.

We begin by briefly stating the main arguments that morally justify the transformation to a learning health care system. The justification builds upon and complements the arguments in favor of learning health care that have been provided elsewhere.<sup>11</sup> We then describe what we mean by a learning activity and the structure of what we call the learning health care system ethics framework. This description is followed by an analysis of each of the framework's seven major elements. Each element is stated as an independent obligation. We consider how each element is similar to or different from requirements prevalent in contemporary research ethics and clinical ethics. We conclude with a discussion of some of the next steps needed to explicate how the framework can be used to guide the ethics of learning in a learning health care system.

## **A Moral Justification of the Learning Health Care System**

The traditional principles that provide the moral grounding for human subjects protection in the United States became cemented as the cornerstones of research ethics in the 1970s<sup>12</sup> during a period of intense societal focus on civil rights and on egregious violations of rights that occurred in highly publicized research scandals. Since the 1970s, the dominant concern has been to protect patients and other subjects from risk, abuse, and unjust distributions of the burdens of research.

An ethical imperative that was less central in bioethics in the 1970s—namely, the establishment of a just health care system—provides an important moral reason, generally overlooked, for a rapid transformation to a learning health care system. There is considerable disagreement about the design of a just health care system and how health care should be organized and financed to achieve it, but arguably there is broad agreement that, at minimum, a just system is one in which present and future generations are able to access adequate health care services without the imposition of undue financial burdens on patients and their families. The obstacles to securing a just health care system, so defined, are complex and include cultural, economic, and political as well as scientific and public health challenges. That said, securing just health care requires a constantly updated body of evidence about the effectiveness and value of health care interventions and of alternative ways to deliver and finance health care. A learning health care system is critical to the efficient and systematic collection and dissemination of this evidence, and we think it is a necessary condition of achieving the goal of creating and maintaining a just health care system.

The societal goal of a just health care system provides only one of three independent and equally important ethical justifications for the transition to learning health care systems. The other two are the goals of high-quality health care and economic well-being. By “high-quality health care” we mean, at minimum, technically competent health care that is based on the strongest clinical evidence and is delivered with the highest achievable patient safety. By “economic well-being” we mean, at minimum, a society in which current and future generations have the economic resources necessary to live a decent human life over the course of the life span. The im-

**Table I.  
Learning Health Care System Ethics Framework**

<i>Obligation</i>	<i>Parties Bearing the Obligation</i>	<i>Synopsis of the Obligation for Learning Activities</i>
<b>Respect the rights and dignity of patients<sup>1</sup></b>	<ul style="list-style-type: none"> <li>• researchers</li> <li>• clinicians</li> <li>• health care systems administrators</li> <li>• payers</li> <li>• purchasers</li> </ul>	<ul style="list-style-type: none"> <li>• Assess the impact of a learning activity on the rights, respect, and dignity of patients</li> <li>• Assess whether a learning activity limits patient choice, as well as the value to patients of any choices so affected</li> </ul>
<b>Respect clinician judgments</b>	<ul style="list-style-type: none"> <li>• researchers</li> <li>• health care systems administrators</li> <li>• payers</li> <li>• purchasers</li> </ul>	<ul style="list-style-type: none"> <li>• Assess the impact of a learning activity on the exercise of clinician judgment</li> <li>• Assess the importance of any restriction on the exercise of clinician judgment for the health and autonomy interests of patients</li> </ul>
<b>Provide optimal clinical care to each patient</b>	<ul style="list-style-type: none"> <li>• researchers<sup>2</sup></li> <li>• clinicians</li> <li>• health care systems administrators</li> <li>• payers</li> <li>• purchasers</li> </ul>	<ul style="list-style-type: none"> <li>• Assess the expected net clinical benefit for patients affected by the learning activity, compared to the net clinical benefit they likely would have experienced if their clinical care had not been affected by the learning activity</li> </ul>
<b>Avoid imposing nonclinical risks and burdens on patients</b>	<ul style="list-style-type: none"> <li>• researchers</li> <li>• clinicians</li> <li>• health care systems administrators</li> <li>• payers</li> <li>• purchasers</li> </ul>	<ul style="list-style-type: none"> <li>• Assess the nonclinical risks and burdens to patients affected by a learning activity, compared to the nonclinical risks and burdens they likely would have experienced if they had not been affected by the learning activity</li> </ul>
<b>Address health inequalities</b>	<ul style="list-style-type: none"> <li>• researchers</li> <li>• clinicians</li> <li>• health care systems administrators</li> <li>• payers</li> <li>• purchasers</li> </ul>	<ul style="list-style-type: none"> <li>• Assess whether the risks and burdens of a learning activity will fall disproportionately on patients who are already disadvantaged</li> <li>• Assess whether the learning activity will disproportionately benefit patients who are already socially and economically advantaged</li> <li>• Assess whether a learning activity will help advance the goal of reducing unjust inequalities in health and health care or can be designed to do so</li> </ul>
<b>Conduct continuous learning activities that improve the quality of clinical care and health care systems</b>	<ul style="list-style-type: none"> <li>• researchers</li> <li>• clinicians</li> <li>• health care systems administrators</li> <li>• payers</li> <li>• purchasers</li> </ul>	<ul style="list-style-type: none"> <li>• Conduct and contribute to learning activities as a matter of role-specific, professional responsibility</li> <li>• Assess the extent to which a learning activity will likely contribute to the quality, fairness, or value of health care services and systems by assessing the soundness of the learning activity's objectives, design, and plans for dissemination and implementation</li> </ul>
<b>Contribute to the common purpose of improving the quality and value of clinical care and health care systems</b>	<ul style="list-style-type: none"> <li>• patients</li> </ul>	<ul style="list-style-type: none"> <li>• Participate in learning activities that are consonant with other obligations in the framework intended to respect the rights and interests of patients; participate in activities deemed acceptable to go forward without patients' express informed consent</li> <li>• Consider participation in learning activities that because of their impact on the framework's other obligations cannot ethically go forward without express informed consent</li> </ul>

<sup>1</sup>This framework has implications for family members, loved ones, and surrogates of patients. Both the first and the seventh obligation extend to family members, loved ones, and surrogates when patients are children or adults whose competence is permanently or temporarily compromised and when adult patients want or need their loved ones to be involved in their care.

<sup>2</sup>If researchers do not otherwise have clinical duties to the patients who are affected by a learning activity, then they do not shoulder an obligation to provide patients with optimal clinical care.

*We should assess both whether a learning activity unduly limits the choices of patients and the value of those choices to patients. Many decisions in health care are not likely to engage values of central importance to the patient.*

portance of efficient and real-time learning to the securing of quality health care is indisputable. The relationship between learning in health care and economic well-being is perhaps less apparent but is arguably as important. Broad agreement exists that the pace at which U.S. health care costs continue to escalate constitutes a serious threat to the economic prospects of the country, individuals, and families; continuous, efficient learning in health care is essential (though not sufficient) to the slowing of this pace and thus to economic well-being.<sup>13</sup>

The goals of just health care, high-quality health care, and economic well-being provide independent moral reasons for the transformation of current health care organizations into learning health care systems. These goals underlie our aim in this paper to present a framework of moral obligations that both integrates and alters some basic ideas in our current research ethics and clinical ethics paradigms. For some readers, the need to improve health care quality may be the most important reason for the transition to a learning health care system, and possibly even the only justificatory reason they accept. This rationale is narrower than our three-reasons approach, but in no way undermines the moral imperative to move to learning health care systems. The improvement of health care quality is a sufficient reason alone. So, too, is a commitment to ensuring economic well-being.

### **What Counts as a Learning Activity?**

A learning activity is one that both 1) involves the delivery of health care services or uses individual health information, and 2) has a targeted objective of learning how to improve clinical practice or the value, quality, or efficiency of the systems, institutions, and modalities through which health care services are provided. All such activities are learning activities, even if they have typically been categorized as clinical research, clinical trials, comparative effectiveness research, quality improvement research, quality improvement practice, patient safety practice, health care operations, quality assurance, or evidence-based management. We do not contest these labels or classification schemes, but they also do not control or influence our analysis. For our purposes, they are all “learning activities.”

Health care services include a wide range of interventions and interactions in which professionals are involved with patients, sometimes over long periods of time. They include

encounters between patients and health care professionals in the traditional settings in which clinical services are provided, as well as in settings such as patients’ homes, pharmacies, and the workplace, and they may occur virtually through telemedicine or other Internet-based modalities. Health information includes any information that relates to an individual’s physical or mental health, the health care services provided to an individual, or the payment for an individual’s health care, whether in the past, present, or future.<sup>14</sup>

### **The Basic Structure of the Framework**

The framework we propose consists of seven obligations: 1) to respect the rights and dignity of patients; 2) to respect the clinical judgment of clinicians; 3) to provide optimal care to each patient; 4) to avoid imposing nonclinical risks and burdens on patients; 5) to reduce health inequalities among populations; 6) to conduct responsible activities that foster learning from clinical care and clinical information; and 7) to contribute to the common purpose of improving the quality and value of clinical care and health care systems.

Respecting patient rights and dignity and avoiding nonclinical risks (obligations 1 and 4) appear in most contemporary discussions of research ethics. Respecting the judgment of clinicians and providing patients with optimal clinical care (obligations 2 and 3) are presuppositions of traditional medical ethics—as, for example, in the influential catalogue of norms in Thomas Percival’s classic volume, *Medical Ethics*.<sup>15</sup> Variations of these four obligations are prominent in contemporary discussions of medical professionalism,<sup>16</sup> and they remain relevant in our framework. However, we also give each an interpretation not found in codified principles of either clinical ethics or research ethics.

Obligations 5, 6, and 7 are specific to the learning health care system context. These three obligations substantially revise traditional conceptions of the moral foundations of research ethics and clinical ethics. Obligations 5 and 6 have more than one obligation-bearer, as presented in Table 1, with the obligations falling on clinicians, investigators, health care institutions, those responsible for institutional policies and practices, payers, and purchasers. Patients are the obligation-bearers in obligation 7, which proposes to sharply reform current rules and guidelines. This obligation placed on patients to contribute, under limited and appropriate condi-

tions, to learning that is integrated with their clinical care is not present in conventional accounts of either clinical ethics or research ethics, where the assumption is that no such obligation exists.

All seven obligations are relevant to judgments about the ways in which a learning activity can negatively or positively affect the rights or interests of patients and professionals. The term “rights” refers to justified claims to something that individuals and groups can legitimately assert against other individuals or groups. The associated term “interests” refers to that which is in an individual’s interest—that is, that which supports an individual’s well-being or welfare in a given circumstance. We use the term “risk” to refer exclusively to a risk of “harm,” meaning a thwarting, defeating, or setting back of an individual’s interests.<sup>17</sup>

### Seven Fundamental Obligations

Each of the seven obligations in the framework constitutes a necessary condition, within a learning health care system, of an adequate ethics. In the absence of any one of these obligations, the framework would lose a basic norm, rendering the framework deficient. However, we do not claim that this set of obligations establishes a set of sufficient conditions in a comprehensive ethical framework. Future work can be expected to specify these abstract rules to provide more granular guidance for institutions and their specific contexts and to perhaps add additional general obligations.

The seven norms presented below have some overlapping content, but no one norm can be reduced to one or more of the others. They are not morally weighted or placed in a hierarchical order of importance. Questions of weight and priority can be assessed only in specific contexts. When these norms come into conflict in particular learning activities, the goal will be to show either that one norm is of overriding importance in that context or that at least some demands of each of the conflicting norms can be satisfied, whereas others cannot.

*1) The obligation to respect patients.* Moral obligations to respect the rights and dignity of persons are not controversial in either clinical ethics or research ethics.<sup>18</sup> Examples of respecting rights include obtaining informed consent, soliciting and accepting advance directives, protecting the confidentiality of health information, and evaluating the effectiveness of health care in terms of outcomes that matter to patients. Respecting the dignity of patients requires health professionals to express respectful attitudes and to treat patients as having an inherent moral worth by, for example, helping patients understand what is happening to them and following the lead of patients in involving their families and friends in their care.

Among the rights most discussed in research ethics and clinical ethics is the right to have one’s autonomy respected.

The obligation to respect patient autonomy is also central to the framework we are proposing, but unlike some bioethics literature, the framework does not give it undue deference or overriding importance.<sup>19</sup> Respecting autonomy is primarily about allowing persons to shape the basic course of their lives in line with their values and independent of the control of others.<sup>20</sup> Not all health care decisions are likely to be attached to a significant autonomy interest of individual patients, and deference of the wrong sort can constitute a moral failure to take adequate care of patients rather than an instance of showing respect.

In interpreting the obligation to respect autonomy in learning health care contexts, we should assess both whether a learning activity unduly limits the choices of patients and the value of those choices to patients. Many decisions in health care—such as how often simple laboratory tests should be repeated during a hospitalization or whether medications should be dispensed by one qualified professional or another—are not likely to engage values of central importance to the patient.<sup>21</sup> Learning activities that relate to such decisions can be undertaken by health professionals and institutional officials without a violation of obligations to respect the rights or dignity of patients.

*2) The obligation to respect clinician judgment.* The importance of clinician judgment to professional practice is well established, although what is meant by clinician judgment is not always clear. We use the term “judgment” broadly to mean the clinician’s considered beliefs about how best to care for a patient in light of multiple considerations and influences, including personal professional experience, the experience of colleagues and mentors, scientific evidence, and the clinician’s understanding of the patient’s values and priorities. Respect for clinicians’ judgments is justified for two reasons. First, the exercise of clinical judgment can further the health interests of patients in achieving the best clinical outcome.<sup>22</sup> Second, the exercise of clinical judgment can advance the autonomy interests of patients because clinicians are often well positioned to ascertain and be responsive to their values and preferences.

Not all constraints on the behavior of clinicians—such as requirements to write notes for a supervisor or to use a uniform method for dosing orders—interfere with the exercise of clinician judgment. Some other constraints interfere with the exercise of clinician judgment, but to varying degrees. For example, formularies requiring physicians to prescribe only one branded drug among several in the same class may have little if any negative impact on the health and autonomy interests of patients that respect for clinician judgment is intended to serve. Learning activities that impose constraints of these types would be compatible with the obligation to respect clinician judgment.

*When learning activities target areas in which there is clinical uncertainty about best practices or limited empirical evidence, the importance of respecting clinician judgment is weakened.*

One problem with the obligation to respect clinician judgments is that even the most well-intentioned judgments of clinicians can be subject to some form of bias.<sup>23</sup> A key precept of evidence-based medicine is that clinician judgment may not result in the best health outcomes for patients, especially when there is an absence of good empirical evidence or that evidence does not factor in the forming of the judgment. Evaluating the strength of the obligation to respect clinician judgment usually entails a contextual assessment of the likely impact of any proposed restriction on the exercise of clinician judgment on patients' health or autonomy interests. When learning activities target areas in which there is clinical uncertainty about best practices or limited empirical evidence, the likelihood that unrestricted clinician judgment will advance the health interests of patients is lessened, and the importance of respecting clinician judgment is weakened. For example, for most patients, there is currently little empirical evidence to support a clinician's judgment that a particular first-line hypertension drug is better than another. The obligation to respect clinician judgment in this context is not as stringent as in a case where clinician judgment is based on more robust evidence or is responsive to patient preferences for different therapeutic options.

**3) *The obligation to provide optimal care to each patient.*** Obligations to promote the welfare of others take on specific forms in health care, usually formulated as role obligations. Professional codes underscore the moral responsibilities of professionals to advance the welfare interests of each patient by providing the patient with optimal care aimed at securing the best possible clinical outcome. "Clinical outcome" encompasses the interests patients have in the promotion, preservation, and restoration of their health and the mitigation of pain, suffering, and disability. During the course of clinical care, clinical risks of setbacks to the health interests of patients are often present. These risks are morally justified if they are outweighed by the prospect of corresponding clinical benefits. Accordingly, clinical care can be ethically acceptable when significant risks are present, as long as the potential or expected benefit to the patient justifies the risk.

A central moral consideration in assessing the ethical acceptability of a learning activity is how the expected net clinical benefit for the patients affected by a learning activity compares to the net benefit they likely would have experi-

enced if their care had not been affected by that activity. In assessing net clinical benefit, the risks in routine clinical practice should be considered. Some learning activities are likely to increase the prospects for net clinical benefit, whereas others are likely to decrease it. An activity designed to evaluate the impact of a computer-generated prompt to clinicians to double-check medication dosage may itself have a positive impact on the net clinical benefits for patients; it may reduce the risk that they will be harmed by a medical error. By contrast, depending on the context, a randomized clinical trial of a first-in-class medication may decrease patients' prospects for net clinical benefit relative to what would be expected if these patients receive approved medical therapies. Other learning activities—such as a prospective observational study that relies only on electronic health data to compare widely used interventions—are likely to have no appreciable effects on net clinical benefit. Accordingly, the impact of a learning activity on net clinical benefit is specific to the particulars of the activity and the related clinical context, but it is morally essential that such assessments be made in a learning health care context.

**4) *The obligation to avoid imposing nonclinical risks and burdens.*** Health care focuses on the health-related interests of patients and the reduction of risks of health-related harms, but obligations to avoid inflicting other kinds of harm and burden also apply in health care. Clinical care and clinical information can be provided or used in ways that affect patients' interests in financial well-being, social standing and reputation, employment and insurance opportunities, dignity, privacy, and the joy of spending time with family and loved ones.

The impact of a learning activity in imposing nonclinical risks and burdens—in comparison to the nonclinical risks and burdens that the patients could be expected to experience if their clinical care did not involve the learning activity—is a moral consideration. For example, the risk that health information will be disclosed inappropriately sometimes increases as a result of a learning activity, and such disclosures can be monitored and reduced through security protections. Learning activities also may impose burdens beyond those needed for patients' usual clinical care, such as extra visits to clinical facilities.

5) *The obligation to address unjust inequalities.* Our framework is rooted in a broader conception of obligations of justice than the conception that dominates traditional research ethics. Fundamental to traditional formulations and to the regulation of research are moral requirements that subject selection be fair and that the distribution of research benefits and burdens be just.<sup>24</sup> Our framework supports the commitment to these injunctions, which are historically rooted in concerns about the abuse of disadvantaged or vulnerable subjects in research. However, these injunctions carve out only a piece of the territory of justice that needs to be considered in the ethics of a learning health care system.

In agreement with the traditional conception, our framework sets a presumptive bar against learning activities whose potential negative effects—including imposition of non-clinical burdens or the worsening of prospects for net clinical benefit—fall disproportionately on socially and economically disadvantaged patients or groups of patients. This bar protects many individuals who are homeless, poorly educated, belong to groups that have been subject to historical and continuing prejudicial treatment, or lack access to health care and physicians. Also in need of monitoring are learning activities whose positive outcomes will disproportionately benefit patients who are already socially and economically advantaged—for example, activities that rely on access to the Internet in the home. This obligation requires those who propose learning activities to consider whether the activity can be carried out in such a way that its benefits extend to the less privileged.

In ways more expansive than traditional conceptions, the learning health care system ethics framework also imposes an affirmative obligation to direct learning activities toward aggressive efforts to reduce or eliminate unfair or unacceptable inequalities in the evidence base available for clinical decision-making, in health care outcomes, and in the respectfulness with which health care is delivered. For example, it is widely acknowledged that pregnant women often respond to medications differently than other adults, but the health needs of pregnant women are rarely the focus of clinical investigation because of concerns about the impact of the medications on the fetus. A learning health care system is well positioned to identify—and should mount—ethically acceptable learning activities to address what some have identified as unjust paucity of evidence about the management of chronic illness in pregnant women.<sup>25</sup>

Learning activities also should target disparities in clinical outcomes associated with widening educational differences in adult mortality from such health conditions as lung cancer and heart disease.<sup>26</sup> Similarly, learning activities should find strategies to reduce the disrespectful ways in which patients in sickle-cell crisis are sometimes treated when they seek pain relief in emergency rooms. Unlike other patients presenting in severe pain, these patients, who are largely young African Americans and thus subject to unjust racial stereotyping, are

often treated with suspicion by clinical staff, who view them not as people suffering from a dreadful disease but as drug users hoping to manipulate the system in search of opiates.<sup>27</sup>

Although reasonable people often disagree about precisely which inequalities are unjust and for what reasons,<sup>28</sup> the narrowing of inequalities and the elimination of discrimination in care between minority and majority patients, economically impoverished and economically secure patients, and poorly educated and well-educated patients is a national priority in the United States and in many other countries.<sup>29</sup> The learning health care ethics framework requires that learning activities be assessed to determine whether they perpetuate or exacerbate unjust inequalities and to determine whether they can be structured to advance the goal of reducing or eliminating inequalities and discrimination in health care. This role has not traditionally been at the forefront of the list of obligations of health care institutions, where these problems of unjust inequalities have been widely overlooked.

6) *The obligation to conduct continuous learning activities that improve the quality of clinical care and health care systems.* The third obligation of our framework—to provide each patient optimal clinical care—has been linked to clinical ethics requirements that clinicians stay current in their knowledge and their skills.<sup>30</sup> Until recently, there has been little discussion of the need to augment this obligation with an affirmative responsibility on the part of clinicians to contribute to that knowledge base.<sup>31</sup> This sixth obligation makes contribution to learning morally obligatory. It also extends its reach beyond health care professionals to institutions, payers, and purchasers of health care. We envision an unprecedented transformation of responsibilities in a learning health care system that applies to physicians in private practice, pharmaceutical companies, private hospitals, and so on. Because health care professionals, officials of health care institutions, and purchasers of health care have unique access to and control over clinical care and health information, they are uniquely positioned to seek, conduct, and contribute to learning activities that can advance health care quality, economic viability, and a just health care system. No other individuals, professionals, or institutions in society have such access or control.

The learning health care system ethics framework makes this sixth obligation foundational in the structuring of health professions and health care institutions. The obligation requires that every practitioner and institution accept a responsibility to feed information into the system that increases our knowledge. Each learning activity to be conducted within the system must be individually assessed for the extent to which it holds out the prospect of contributing to the improvement of health care services and systems. This assessment should include an evaluation of the soundness of the learning activity's objectives, design, and plans for implementation or dissemination. Learning activities today may improve only the

## *Just as health professionals and organizations have an obligation to learn, patients have an obligation to contribute to, participate in, and otherwise facilitate learning.*

specific health care settings in which a learning activity takes place, with only some activities and new information being transportable to a wider body of health care institutions. This current limitation will gradually be transformed into a vast array of interconnected learning activities.

7) *The obligation of patients to contribute to the common purpose of improving the quality and value of clinical care and the health care system.* Traditional codes, declarations, and government reports in research ethics and clinical ethics have never emphasized obligations of patients to contribute to knowledge as research subjects. These traditional presumptions need to change. Just as health professionals and organizations have an obligation to learn, patients have an obligation to contribute to, participate in, and otherwise facilitate learning.

This obligation is justified by what we call a norm of common purpose. This norm of *common purpose* is similar to what John Rawls calls the principle of the *common good*, a principle presiding over matters that affect the interests of everyone.<sup>32</sup> The common interest of members of a society in the health care system is that it be positioned to provide each person in the society with quality health care at a cost compatible with individual and societal economic well-being. We also have a common interest in supporting just institutions, including activities that reduce the unjust inequalities that were mentioned in obligation 5.

Securing these common interests is a shared social purpose that we cannot as individuals achieve. Our goals cannot be reached efficiently without near-universal participation in learning activities, through which patients benefit from the past contributions of other patients whose information has helped advance knowledge and improve care. Patients cannot discharge this obligation merely by paying a fee for the health care service they receive or by contributing to society through taxation or charitable contributions. No amount of money paid for health care services substitutes for direct participation in and contribution to learning activities. The knowledge necessary to secure a high-quality and just health care system cannot be obtained from information limited to a bounded number of patients at discrete points in time. A learning health care system must have continuous access to information about as many patients as possible to be efficient, affordable, fair, and of highest quality.

A related justification for obligation 7 is the reciprocal obligation that arises among strangers who occupy the role of patient over time. The philosopher David Hume expresses the general form of this duty of beneficence as follows: “All our obligations to do good to society seem to imply something reciprocal. I receive the benefits of society, and therefore ought to promote its interest.”<sup>33</sup> In our framework, the discharge of obligations of reciprocity occurs through an established practice of making an appropriate and proportional return—returning benefit with proportional benefit, with all alike sharing, as a matter of moral obligation, the burdens necessary to produce these benefits.

In proposing that patients have an obligation to contribute to the common purpose of improving health care through learning, we are not proposing that patients have an affirmative moral obligation to participate in all learning activities regardless of the degree of additional risk or burden they may impose. Different learning activities will have differential effects on the rights and interests of patients and therefore will have different implications for patients’ obligations to participate in them. The first four obligations of this framework are intended to protect these rights and interests in the assessment of the overall ethical acceptability of particular learning activities. For example, some learning activities, such as randomized clinical trials of investigational new devices, would not be obligatory because of the potential to fail in meeting obligations 1 through 4. If this type of learning activity is otherwise ethically acceptable, however, then patients might *choose* to participate in it, though they should be informed and understand that they are under no obligation to do so. By contrast, other learning activities—such as participation in a registry, reviews of deidentified medical records, and being interviewed by health care staff to better improve the patient care experience—are likely to be instances in which patients do have an obligation to participate, assuming that the activities have a reasonable likelihood of improving health care quality and that appropriate data security protections are in place. These conditions are probably met currently in integrated health care systems that have invested in secure electronic health records and have mechanisms in place to adjust local norms of care in direct response to the results of learning activities.<sup>34</sup>

The obligation of patients to contribute to health care learning is compatible with duties to inform patients about

learning activities and to solicit their express consent for some learning activities, as appropriate. The first obligation in our framework requires, as a matter of respect, that health care institutions have numerous and varied policies and practices in place to inform patients about the institution's commitment to learning and about the specific learning activities that are currently underway and how they are being conducted. Activities such as randomized, controlled trials of an investigational new device could proceed only with patients' express, affirmative agreement, obtained through a valid informed consent process.

As with the first obligation above, the obligation to contribute to learning can extend to family members, loved ones, and surrogates of patients, particularly when patients are children or adults whose competence is permanently or temporarily compromised. Whenever loved ones are intimately involved in the care of the patient, they may have information or insight critical to learning about and improving health care interventions and processes. For patients lacking cognitive or decisional capacities, loved ones and other surrogates can play a vital role in the ethics framework by representing and protecting patients' interests of during learning activities.

It has several times been asked in the bioethics literature whether there is a duty to serve as a research subject. Some have answered the question affirmatively. Their reasons have been premised on a conception of duties to participate reciprocally in a system that produces public goods from which we all benefit and in which no one should, in this respect, be a free rider.<sup>35</sup> In certain circumstances, even compulsory participation has been proposed.<sup>36</sup> Although similar justice-oriented grounds are central in some of our arguments, we are proposing a more pervasive level of participation, and participation of a different type, than previous writers have recommended. We make it a condition of participating in a learning health care system as a patient that one also participates in the learning activities that are integrated, on an ongoing basis, with the clinical care patients receive.<sup>37</sup> The scope of participation that we are proposing is far more extensive and notably different from than that proposed by previous writers on duties to participate in research.

### **Going Forward with the Learning Health Care System Ethics Framework**

The framework we have proposed for a learning health care system departs significantly from previous frameworks in research and clinical ethics. Its most distinctive features are twofold. First, the framework eschews the moral relevance of the traditional distinction between research and practice in a learning health care environment, focusing attention instead on the moral obligations that should govern an integrated learning health care system. Second, the framework sets a moral presumption in favor of learning, in which health pro-

fessionals and institutions have an affirmative obligation to conduct learning activities and patients have an affirmative obligation to contribute to these activities. This presumption is grounded in the claims that all parties benefit from this arrangement and that the societal goals of health care quality, just health care, and economic well-being require continuous learning through the integration of research and practice.

This framework will help facilitate the transformation to a learning health care system. Going forward, the next step will be to specify the framework's implications for oversight policies and practices, including prior review and informed consent, and to determine precisely how the framework will interact with the current human subjects regulations and institutional review board system. Given that our framework rejects the moral relevance of the traditional distinction between research and practice in a learning health care system, different operational criteria for determining which activities should be subject to oversight policies, based on the seven moral obligations, will need watchful development. For example, future work will need to use multiple criteria to determine which activities require express prospective consent and which may be addressed by routine disclosures. Critical to this work is canvassing the views of patients and other stakeholders—an effort that is already under way.<sup>38</sup> Although the hard work of specifying the policies and practices needed to implement the framework is just beginning, we close with a few preliminary observations—first, about the implications of the framework for clinical practice, and second, about the operationalization of the first and seventh obligations.

As we argue in the first article in this set, the underprotection of patients from unjustified and often preventable harms and burdens in clinical practice is a profoundly serious moral problem. We are not proposing, nor do we think it correct, that the solution to the underprotection problem is simply to expand the current review system for research. Multiple conditions and factors contribute to the underprotection problem, and a complex set of strategies will be needed to address the problem effectively. The learning health care ethics framework is intended to be one part of the solution. First, the framework makes obligatory the kinds of learning that are necessary to reduce the harms that occur in clinical environments and resolve the uncertainties that exist around many clinical practices. Second, the framework makes such learning easier to conduct; by reducing the overprotection of patients from learning activities that do not undermine their interests or rights, it facilitates learning that can help address the underprotection of patients in clinical practice. Put slightly differently, insofar as contemporary research ethics and oversight interfere with learning activities that could reduce errors and improve clinical effectiveness, the overprotection that results is itself a source of harm to patients' interests.

Health care institutions and clinicians are constantly adopting new practices, ranging from platforms to support

clinical decision-making built on electronic health systems to minimally invasive and robotic surgery. These innovations are often introduced without systematic assessment of their impact, perhaps to avoid crossing the unwelcome and curious divide between practice and research. Our framework makes this distinction irrelevant to questions of oversight and provides reasons why health care institutions and professionals are obligated to accompany the introduction of such innovations—as well as practices that have never been rigorously evaluated—with a commitment to systematically learn about their effects on clinical outcomes, health care value, patients' experience, and health disparities.

We envision that a learning health care system will adopt an array of policies and practices that provide a moral link between the first obligation—to respect the rights and dignity of patients—with the seventh obligation—that patients contribute to the common purpose of improving the quality of clinical care and the health care system. For example, the learning health care system would disclose to patients in multiple ways and at various times that learning occurs constantly throughout the health care system, and that the products of such learning are constantly updated and integrated into the system of care. Concrete examples would be provided of how care has been improved as a result of learning. Such disclosure serves to underscore to patients the system's moral commitment to continuous learning, the relationship of that learning to the quality of care they will receive, and the system's commitment to ensuring that patients are aware of continuing learning activities and their risks and benefits. Disclosure procedures might include information provided at initial interviews or at enrollment, in postings in waiting rooms, and in newsletters and Web sites. The best ways to communicate with patients must be identified and evaluated, and these approaches to disclosure should be shared with small hospitals and practices without the resources to do so on their own.

The health care system would likewise inform patients in routine and systematic ways of the policies that are in place to provide ethical oversight of learning activities, as well as how the confidentiality of their medical information will be maintained, how privacy is insured, how information is transmitted to other health care institutions, and the like. There would also be transparency in the conduct of learning activities. Transparency might be achieved by, for example, listing the steady flow of learning activities on system Web sites (and on paper, if requested) and by accountability to the public and to patients regarding what is learned in these activities, including whether and how a learning activity has improved clinical practice. In addition, a learning health care system would publicize to patients that, while they might not be informed routinely about each learning activity—since many have little, if any, effect on patients' interests or rights—they will be adequately informed, and their consent sought, when-

ever a learning activity might have a negative impact on the quality of care or impose burdens above and beyond what they would otherwise experience.

Finally, we appreciate that the learning health care system ethics framework we have proposed will be criticized as a premature and overly extensive reshaping of traditional research ethics and clinical ethics. Others may think we propose too little. We claim no more than a start on a subject that merits extensive investigation, and we welcome suggestions and commentary moving forward. The transformation to a learning health care system is still in its infancy. We are in the early days of a progressive realization of a lofty aspirational goal, but given the preventable harm, waste, and uncertainty about clinical effectiveness in health care, efforts to accelerate learning should be given high priority. Now is a good time to lay the ethical foundations of a learning health care system and to begin work on its specific moral commitments.

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36. See Harris, "Scientific Research is a Moral Duty," 244-45, together with a defense and reformulation of the position in S. Chan and J. Harris, "Free Riders and Pious Sons: Why Science Research Remains Obligatory," *Bioethics* 23, no. 3 (2009): 161-71; and a criticism of Harris and Chan in I. Brassington, "Defending the Duty to Research," *Bioethics* 25, no. 1 (2011): 21-26.
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# A Prescription for Ethical Learning

BY EMILY A. LARGENT, FRANKLIN G. MILLER, AND STEVEN JOFFE

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Learning health care systems combine observational and comparative effectiveness research with the delivery of medical care.<sup>1</sup> Integration of research and care within such systems promises to facilitate the practice of evidence-based medicine and to advance socially valuable research, yielding individual and collective benefits for current and future patients. We argued last year in this journal that extensive integration of research and care is a worthy goal of health system design, and we second the call from Ruth Faden and colleagues to move toward learning health care systems.<sup>2</sup>

As they recognize, learning health care systems demand the coordination of research and medical ethics—two sets of normative commitments that have long been considered distinct. In offering a novel ethics framework for such systems, Faden et al. advance the scholarly debate about how best to do this and challenge us to think more deeply about its practical implications.

Their argument moves in the right direction, but we believe that at least three issues they raise require additional attention. First, the research-care distinction has more normative bite than they are willing to concede. Second, the role for independent oversight requires clarification. Finally, they neglect the concept of stewardship as a guiding obligation of learning health care systems.

The work of Faden and colleagues is motivated in part by the belief that current oversight systems for research hamper some low-risk health-related research, whereas the regulatory systems for health care often fail to protect against risks associated with routine medical care. One premise of their argu-

ment is that the justification of formal research oversight rests on the empirically assailable assumption that “research with patients often introduces risks, burdens, or inconveniences that are unrelated to patients’ clinical care needs (and that no comparable clinically irrelevant risks or burdens are imposed in clinical care outside of research).” They note correctly that not all research carries net risks, and conversely that clinical care is riddled with potentially harmful activities that hold no prospect of compensating benefit for patients.

It is important, however, to differentiate the empirical and the normative dimensions of the research-care distinction. Risks and burdens of clinical practice that derive from poorly designed systems or inadequate practice, and that are therefore not justified by benefits to patients in light of current knowledge, are morally objectionable. By contrast, it is *not* morally objectionable when clinical research exposes informed and consenting participants—whether patients or healthy volunteers—to modest net risks justified by potential benefits to future patients and society. Indeed, such risks are inherent in the practice of research. The moral distinction between human experimentation and standard medical care is therefore still relevant despite empirical data suggesting that the risk-benefit ratios of these practices often converge. The validity of this distinction is nevertheless compatible with acknowledging that, in learning health care systems, the pursuit of generalizable knowledge no longer accurately differentiates research from care.

The distinction’s enduring validity is illustrated by some problems in how the authors formulate elements of their normative framework for learning health care systems. Consider the third obligation in the new framework they propose: to provide “the patient with optimal care aimed at securing the best possible clinical outcome.” Aiming for an optimal outcome seems inherently at odds with interventions that impose more than minimal net risks for patients justified by the potential social benefits. Strictly interpreted, obligation four of the proposed framework—“to avoid imposing nonclinical risks and burdens”—rules out any research integrated with medical care that poses net risks or burdens, no matter how minor, on patients.

Faden and colleagues also deliberately leave the role of independent oversight in a learning health care system unspecified. We can envision at least three possible approaches to oversight: 1) prospective review of most or all learning activities, akin to the current system; 2) prospective review of a subset of learning activities, perhaps those that impose greater than a defined threshold of net risk; or 3) abandonment of the requirement for independent review. We are skeptical that independent review is any less relevant in the context of a

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## *The moral distinction between human experimentation and standard medical care is still relevant despite data suggesting that the risk-benefit ratios of these practices often converge.*

learning health care system than in the current system. First, the reason for independent review is to exercise oversight of activities that impose net risks and research-related burdens, activities that will necessarily persist in a learning health care system. Here again we see the importance of the research-care distinction, for if we abandon this distinction, how will we identify the subset of activities that should be subject to review? Second, even in a system that optimally integrates research and care, we must not lapse into “the therapeutic orientation” to clinical research and obscure the fact that clinical research sometimes involves exposing subjects to net risks or burdens for the sake of generating knowledge.<sup>3</sup> To deny a role for independent review is to deny the possibility of a risk-knowledge tradeoff. Nevertheless, we agree that independent review might evolve to become narrower in scope, more flexible, and better adapted to this environment than the current system of institutional review boards.

The authors extol pediatric oncology as a model for integrating research and care. The substantial benefits of integration for pediatric cancer patients as a class notwithstanding, this context reinforces both the salience of the ethical distinction between research and care and the need for independent oversight. The fact that most children with cancer receive their care in the context of clinical trials should not obscure the difference between validated treatments and experimental treatments undergoing evaluation.<sup>4</sup> Similarly, it is essential to distinguish between procedures performed for diagnostic or therapeutic purposes and procedures, such as research biopsies, that are performed to measure study outcomes. Furthermore, the fact that pediatric oncology has successfully integrated research and care in no way diminishes the need

for independent oversight to ensure a reasonable balance of risks and potential benefits, attention to informed consent, and other core criteria of ethical research.<sup>5</sup>

Finally, we wish to suggest *stewardship* as an additional obligation within an ethical framework for learning health care systems. A praiseworthy objective of such systems is the realization of just, high-value health care. This objective naturally gives rise to responsibilities, which fall on researchers, clinicians, administrators, payers, purchasers, and patients alike, to learn how to use resources as wisely as possible for current and future patients. Although the authors highlight the societal goal of economic well-being as one of three moral justifications for learning health care systems, they impose corresponding obligations only on patients. An explicit commitment to stewardship as a core obligation of all stakeholders within learning health care systems would morally ground learning activities devoted to the identification and adoption of evidence-based, value-promoting practices.

The papers in this supplement are part of an exciting new vein of bioethics scholarship seeking to reconceptualize the relationship between research and care. Although many questions remain, we commend the authors for their valuable contribution and for motivating discussion of the ethical issues raised by the concept of the learning health care system.

### **Disclaimer**

The opinions expressed are those of the authors and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

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# The Unbelievable Rightness of Being in Clinical Trials

BY JERRY MENIKOFF

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All of us involved in bioethics should welcome the involvement of Ruth Faden and colleagues in the evaluation and reforming of the rules for protecting research subjects. In these two articles, they have put together a bold vision of one way to move forward.

First and foremost, it is quite remarkable how much of what they say squarely meshes with the ideas of the U.S. Department of Health and Human Services about reforming the system. Faden and colleagues correctly observe that “a central goal of the health care system is to collect, aggregate, analyze, and learn from patient-level data.” They note that there is a huge amount that can be learned from these activities and that doing so in an appropriate way often poses little risk to patients. That very point is a major theme of DHHS’s recent Advance Notice of Proposed Rulemaking, which discusses numerous possible changes to accomplish the same thing by eliminating or reducing inappropriate burdens on the conduct of these activities.<sup>1</sup> While the DHHS approach takes a different route—it does not involve scrapping the distinction between research and clinical care—it is nonetheless gratifying to see that this prestigious group is in effect endorsing a similar outcome.

Having said that, I want to turn to a very different part of the research universe, the elephant in the room as it were: the world of interventional randomized clinical trials. Under the current regulatory system, these research subjects receive substantial protections. Most importantly, they are generally enrolled only after they give their informed consent. The rationale for this approach is that research subjects are denied

the core ethical protection provided to patients: there is no requirement that everything done to them be in their best interests.

Faden and colleagues appear to be proposing to eliminate this informed consent requirement for a significant range of such trials. They are surprisingly sketchy on the details about which clinical trials would still require informed consent. They allow that randomized, controlled trials of an “investigational new device,” and perhaps of “first-in-class medications,” would still require consent. Interestingly, they make no such comment about, for example, trials involving comparisons of marketed medications being used consistent with Food and Drug Administration–approved labeling. These statements, together with other writings from some of these authors<sup>2</sup> and their observation that their new patient obligation (obligation 7) “sharply reforms” the current rules, suggest that they indeed intend that a substantial segment of current randomized clinical trials—particularly those involving treatments that are already commonly used in clinical care—could fall under their “required participation” category. (Surely their point that participation in registries, reviews of deidentified medical records, and staff interviews would be required is not the “sharp reform,” since many such activities are not even subject to the current regulations.)

What justifies this change? Two key observations about risks and benefits appear to form the core of their arguments. First, they note that medical care is in fact neither as effective nor as safe as we often claim it to be, observing among other things that “mounting evidence indicates that patients in ordinary clinical care are often at risk of receiving suboptimal outcomes and of being harmed, however inadvertently, as a consequence of inadequate evidence, unproven traditional practices, and biases in clinical judgment.” Readers can certainly make their own judgments about whether the acknowledged limitations in the quality of clinical care are substantial enough that they provide a good justification for randomizing patients to treatments without the type of consent currently required.

Their second argument, that “patients in clinical trials [appear to] fare no worse clinically than patients in clinical practice,” cites two meta-analyses from 2001 and 2005. One of those papers notes, among numerous qualifications, that the evidence is “weak.”<sup>3</sup> The other paper observes that there was “significant heterogeneity” among the studies they compared, which they could not explain.<sup>4</sup> (I am told by statistics experts that this should constitute a big red warning light in terms of pooling the outcomes.) Neither paper’s authors suggest their conclusions in any way justify weakening informed consent protections to subjects.

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Jerry Menikoff, “The Unbelievable Rightness of Being in Clinical Trials,” *Ethical Oversight of Learning Health Care Systems, Hastings Center Report Special Report* 43, no. 1 (2013): S30-S31. DOI: 10.1002/hast.136

## *Faden and colleagues seem to suggest that for many clinical trials, there is no good reason for a patient to prefer one arm to the other. Is this true?*

Even hypothetically accepting that, on “average” (which is what these studies are at best showing), subjects in research studies fare no worse (and perhaps even a bit better) than patients receiving care in the clinical setting, what would that mean? Does that provide a particularly good justification for requiring participation in these studies? This “average” outcome is perfectly consistent with the conclusion that there are nonetheless often winners and losers, depending on which study a patient is enrolled in. The study a patient is enrolled in could be one in which there ends up being major differences in mortality or morbidity between the two arms. This is not the sort of thing that averages out for an individual.

Faden and colleagues seem to be suggesting that for many clinical trials that don’t involve a brand-new drug or device (and thus are presumably less “risky”), there is no good reason for a patient (or her doctor) to prefer one arm to the other. Is this true? Often, a study will compare two treatments precisely because we already have some tentative evidence suggesting meaningful differences. (Note, for example, the list of priority areas for comparative effectiveness research put together by the Institute of Medicine.<sup>5</sup>) In many instances, that tentative evidence will give patients good reason to gamble on one option as opposed to the other (particularly when their disease needs immediate treatment and they only have one shot at getting that treatment). It is likely a relatively rare study where there are genuinely no good reasons for a patient or doctor to prefer one treatment over the other.

I fully agree that there are some such studies for which consent may not be necessary. Indeed, the current rules allow waivers of consent, even for some clinical trials. And the government’s proposal to reexamine the rules considers the possibility that some quality improvement studies may additionally not require informed consent. But the authors appear to be making a quantum leap beyond these propositions (having categorized that proposal as too “limited”), implicitly suggesting that a substantial portion of clinical trials could fit into the “no legitimate reason for patient or doctor preference” category. At the least, those proposing a major conceptual reform that could substantially cut back on a patient’s right to choose should present some actual evidence on this crucial point.

In a landmark work published nearly forty years ago, Charles Fried commented on studies that were then taking place in which women with breast cancer were being ran-

domized to radical mastectomy or to less extreme surgery. Those women were not told that their treatment was being chosen by randomization, nor even that they were in a clinical trial. The justification: no one was sure which of the surgical procedures produced better results. Fried firmly rejected that argument: “The system of rights in personal care, applied to experimentation, entails the right to full disclosure, to complete candor, and the right not to be experimented upon against one’s own will, the right to choose one’s own therapy with full awareness of the alternatives.”<sup>6</sup>

It is somewhat ironic to note that among the studies evaluated in one of the meta-analyses cited by Faden and colleagues were comparisons of time to cancer recurrence for mastectomy and breast-preserving surgery. Of course, the meta-analyses, in determining that “average” outcomes were no worse in the clinical trials, looked only at the average differences in that time to recurrence. Whether an individual woman got to exercise a fully informed right to choose her treatment, and thus, whether she ended up keeping her breast or having it removed, was not even on the radar screen of the meta-analyses.

For decades now, we have had the system Fried envisioned, protecting the rights of subjects in clinical trials to make their own such choices, even where the two treatments being studied were in equipoise. Now we face an apparent attempt to dramatically move our system back to what was happening in Fried’s time, based on arguments not dissimilar to those he rejected. Have conditions changed so much that what has long been considered unethical now is ethical?

### **Disclaimer**

The views expressed in this commentary are solely those of the author and do not represent the official position of the U.S. Department of Health and Human Services or its division, the Office of the Assistant Secretary for Health.

1. Department of Health and Human Services, “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators,” *Federal Register* 76, no. 143 (2011): 44512-31.

2. See N. Kass, R. Faden, and S. Tunis, “Addressing Low-Risk Comparative Effectiveness Research in Proposed Changes to U.S. Federal Regulations Governing Research,” *Journal of the American Medical Association* 307 (2012): 1589-90.

3. D.A. Braunholtz, S.L.J. Edwards, and R.J. Lilford, “Are Randomized Clinical Trials Good for Us (in the Short Term)? Evidence for a ‘Trial Effect,’” *Journal of Clinical Epidemiology* 54, no. 3 (2001): 217-24.

4. G.E. Vist et al., “Systematic Review to Determine Whether Participation in a Trial Influences Outcome,” *British Medical Journal* 330 (2005): 1175-81.

5. Institute of Medicine, Committee on Comparative Effectiveness Research Prioritization, *Initial National Priorities for Comparative Effectiveness Research* (Washington D.C.: National Academies Press, 2009).

6. C. Fried, *Medical Experimentation: Personal Integrity and Social Policy* (New York: American Elsevier, 1974).

# Making the Transition to a Learning Health Care System

BY CHRISTINE GRADY AND  
DAVID WENDLER

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The past decade has seen increased awareness of the importance of creating and sustaining health care systems in which the collection of data and the generation of knowledge are “embedded into the core of the practice of medicine.”<sup>1</sup> This emphasis on “learning” health care systems includes quality improvement projects, comparative effectiveness research, creation of registries, and other activities that collect information in the service of improving health care quality while reducing waste, cost, and complexity.

The authors of the two main articles in this supplement recognize the enormous potential of learning health care systems. Their first article argues that the development of these systems calls into question existing guidelines and practices that treat clinical care and clinical research as distinct activities. Their second article proposes to replace this traditional approach with a new framework, one intended to promote two important goals: support the transformation to a learning health care system and help to ensure the ethical appropriateness of the activities carried out within such a system. To promote these goals, the authors propose a framework consisting of seven obligations: 1) respect patients’ rights and dignity, 2) respect clinicians’ judgment, 3) provide optimal care to each patient, 4) avoid imposing nonclinical risks and burdens, 5) reduce unjust health inequalities, 6) conduct learning activities, and 7) contribute to efforts to improve health care.

As the authors note, the first four obligations are not well and, absent significant elaboration and analysis, provide little

guidance on how to promote the second goal of ensuring the ethical appropriateness of the activities carried out within a learning health care system. For example, the authors, like many commentators before them, argue that obtaining informed consent is central to discharging the obligation to respect patients’ rights and dignity. Yet there is wide disagreement regarding when it is necessary to obtain informed consent, and in what form, and using what process. Learning health care systems will thus need guidance on when and in what ways patients should provide informed consent for the learning activities to which they contribute. Should consent be required to use patients’ medical records, or to draw a few extra milliliters of blood, in order to evaluate better ways to provide care for their condition? If so, must this consent be study specific? Is opt-out consent acceptable?

The final three obligations also provide little help for answering these questions. For example, the obligation on the part of patients to contribute to learning activities, while relevant, does not clarify for which activities patients’ consent should be required.

The authors are aware that their framework does not provide much guidance for promoting their second goal, and they call for future work to determine which policies and practices should be adopted by learning health care systems, including policies and practices regarding review and informed consent. At first glance, the seven obligations also might appear to offer little in the way of promoting the first goal of supporting the transformation to a learning health care system. Commentators who accept the traditional distinction between research and care could endorse—indeed, many likely do endorse—all seven obligations. They certainly endorse the first four obligations—to respect patients’ rights and clinicians’ judgment, and to provide optimal care and minimize nonclinical risks.

Commentators who accept the traditional distinction between research and care also have argued for the fifth obligation—to address unjust health inequalities, especially unjust inequalities that persist between developed and developing countries.<sup>2</sup> And a number of these commentators have argued that there is an obligation on patients to participate in clinical research.<sup>3</sup> In what way, then, is the proposed framework novel and transformative, as the authors claim? The answer appears to lie largely in how the authors interpret the sixth obligation in the framework—the obligation to conduct learning activities.

Those who endorse the traditional distinction between research and care would likely interpret this obligation as applying to clinicians who can discharge it by occasionally

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*On the authors' interpretation, people involved in health care are obligated to work to essentially maximize the extent to which they contribute to learning activities.*

supporting and participating in learning activities, perhaps referring some patients to a clinical trial or participating as a site in a phase III study. The authors of the present work, in contrast, endorse an interpretation of this obligation that is much broader, in that it applies to a wider range of individuals, and much stronger, in that it requires more of them. They claim that this obligation applies to *essentially everyone* involved in health care: clinicians, including those who work in private practice, private hospitals, and pharmaceutical companies, as well as health care institutions, people responsible for health care institutional policies and practices, payers, and purchasers. Moreover, on the authors' interpretation, these individuals are obligated to work to *essentially maximize* the extent to which they contribute to learning activities. It is not enough to contribute to learning in some ways and at some times. Instead, essentially everyone involved in health care is obligated to work toward the goal of continuously participating in learning activities.

This interpretation of the sixth obligation appears to have dramatic implications. It suggests that nurses and physicians who focus on what many have argued is the primary obligation of clinicians—do what is best for the patient in front of them—are in an important sense acting unethically unless the patients' treatment and results are integrated into learning activities designed to benefit future patients. Similarly, this interpretation seems to suggest that pharmaceutical companies and the clinicians who work for them have an ethical obligation to participate in an “unprecedented transformation” of essentially all of health care into a “vast array of interconnected learning activities.”

The transformative nature of the authors' proposal is emphasized by the claim that not only do essentially all those involved in health care have a moral obligation to continuously participate in learning health care activities, but that, following the fifth obligation, they have an “affirmative obligation to address learning activities toward reducing or eliminating unfair or unacceptable inequalities.” While the goal of a more just health care system is laudable in its own right, it seems tangential to the goal of integrating research and care, and it

may complicate the question of how and by whom the proposed ethical framework is intended to be used. Must large pharmaceutical companies focus their learning endeavors on those with the potential to reduce inequality and increase justice in health care? If so, it will be vital to determine whether this obligation is an enforceable one that pharmaceutical companies can be legally required to discharge. Or consider a small community hospital in an affluent region that seeks to adopt a learning health care system in order to improve the quality of care delivered to its clientele. Can it move forward, given that its activities may well increase the health disparities between rich and poor?

Given the radical nature of the proposal and the extent to which this transformation depends on the authors' very strong interpretation of the sixth obligation, significantly more work will be needed to evaluate and defend this interpretation. The present work appears limited to pointing out that health care professionals are “uniquely positioned to seek, conduct, and contribute to learning activities.” While this seems right, the fact that some individuals are best situated to bring about a desirable outcome does not—absent a good deal of further argument—imply that they are obligated to continually strive to bring about these outcomes.

It should come as no surprise that a good deal of future work will be needed to make the transformation to learning health care systems, especially if the transformation is to be as radical as the authors of these two works envision. We expect their contributions to have a central role in these discussions.

#### **Disclaimer**

The views expressed are the authors' own. They do not represent the views of the National Institutes of Health or the Department of Health and Human Services.

#### **Acknowledgments**

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## Ethical Oversight: *Serving the Best Interests of Patients*

BY JOE V. SELBY AND  
HARLAN M. KRUMHOLZ

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The articles by Nancy Kass, Ruth Faden, and colleagues describe an ethical imperative to study clinical care as it is being delivered. Their case rests on the fact that much of clinical care is currently recommended and delivered with uncertainty. Often, patients, clinicians, and health care systems must make health care choices without knowing enough about the choice to be confident that it aligns well with their preferences and values. The problem is that patient experience is often not leveraged to produce the information that will be needed by future patients, clinicians, and health care systems. The ethical response to this imperative is the learning health care system, in which the collection and analysis of clinical data for quality improvement and comparative effectiveness become the new standard for high-quality clinical care in its ongoing delivery. The premise is that it is both possible and desirable to integrate clinical care and research more seamlessly.

The goal of learning from each patient is attractive, but integrating research and clinical practice is not easy. The authors suggest that the bioethical framework in use for the past forty years to oversee clinical research may be as much an impediment to the development of a learning health care system as a means of protecting the interests of patients. This framework draws a bright line between clinical research and clinical care activities, subjecting clinical research to institutional review and ongoing oversight while assuming that clinical care is conducted primarily in the interests of patients

and not in need of additional ethical oversight. The authors identify five characteristics that have been used to distinguish the two activities, and they conclude that none succeed. The practical implications of this conclusion are left unspecified, however. Should ethical oversight simply be eliminated for these kinds of research activities on the grounds that oversight is not mandated for clinical care and the two cannot be distinguished?

We agree that the first two characteristics—that research is a systematic activity involving planned collection of information, and that its primary aim is to produce knowledge that can be generalized to other patients—fail as distinguishing criteria. The systematic collection of diagnostic, treatment, and outcomes information and generalization from clinical experience in one patient to other patients and settings has always characterized good clinical practice. Astute, ethical clinicians have always aimed to generalize from information on past patients to benefit current patients and, through teaching, the future patients of their students. They have also tried variations on established practice in efforts to detect patient response and test new strategies. It would be ironic if, just as computers, electronic health records, and advanced analytic methods promise to make these time-honored practices more powerful and accurate, they should instead be slowed or stymied by misplaced ethical concerns.

We are less inclined than the authors to dismiss the remaining three characteristics—namely, that research presents less net clinical benefit and greater overall risk than does clinical practice, introduces burdens or risks from activities not otherwise part of patients' clinical management, and replaces individual decision-making with protocols dictating therapeutic or diagnostic choices. We believe that potential research activities, even among quality improvement and comparative effectiveness research studies, vary widely with respect to each of these criteria. The intensity of ethical oversight should be commensurate with the risks and burden imposed.

It is helpful to distinguish the various approaches used in quality improvement and comparative effectiveness research. For this discussion, we identify three broad methodologies: observational studies conducted entirely with existing clinical data, in which generation of research evidence is truly “incidental” to the delivery of care; prospective observational studies, in which some level of additional research-related data collection is introduced into clinical care, but clinical decisions remain entirely in the hands of clinicians and individual patients; and intervention studies, in which treatments are assigned by randomization or related methods, rather than

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by decision-making as it is typically conducted in the clinical encounter.

For observational studies with no additional data collection, only the first two criteria apply, and we have already dismissed these as failing to distinguish research from good clinical care. With a single exception, the remaining three criteria do not apply because these studies do not affect patients or their care. They raise no questions of net benefit or harm, added burdens, or relegation of care decisions to research protocols. The exception is a potential risk to privacy and confidentiality that comes from gathering large amounts of clinical information on individual patients in individually identifiable datasets and from transmitting such data outside the firewalls of host institutions. There are well-established security practices for storing and transmitting research data,<sup>1</sup>

*Potential research activities, even among quality improvement and comparative effectiveness research studies, vary widely with respect to the last three criteria that the authors consider.*

and the track record of research is quite good in this regard. Thus, for this category of research, we agree that review and oversight could be simplified, benefiting patients while lowering research and institutional costs, so long as data storage and transmission practices are adequately monitored by institutions.

For the remaining two categories, we believe that independent bodies—representative of patients, clinicians, the health system, and the research community—should continue to weigh the benefits and risks of proposed studies. Observational research that requires collection of data not otherwise needed for delivery of appropriate care imposes variable degrees of burden on patients, as well as on clinicians and health care systems. Minimally, these burdens include some inconvenience, loss of time, and the financial costs to systems associated with the data collection activities and lost productivity. Both the importance of the research and the magnitude of these burdens vary among studies.

For intervention studies—whether interventions are assigned at the individual patient level or at higher levels, in practices, clinics, or hospitals—personalized decision-making

is, as Robert Levine has explained, replaced with randomly assigned care.<sup>2</sup> Even for low-risk interventions, such as comparisons of two approved and widely used medications or two approaches to care coordination, randomized treatment assignment may fall short of physician-patient decision-making that takes into account patients' clinical and social characteristics, their needs, and their preferences for care options and various outcomes. Someone besides the researchers should participate in considering how likely it is that randomization could lead to worse choices than individual decision-making does. In weighing the potential benefits and risks of the proposed research, this body may consider whether there are possible alternatives to randomization, and must determine whether informed consent is required and, if so, how it should be obtained.

For these latter two categories of research, review will often find, as the authors suggest, that the risks and burdens are low and the potential benefits high. With the ethical imperative to conduct this type of research in mind, the critical issue then becomes how to minimize the burdens of oversight to patients, clinicians, and researchers. A critical determination is whether individual informed consent is required in intervention studies and how complex the consent process should be. Requiring individual informed consent may render important, low-risk studies impossible, especially in the case of large cluster randomized trials.<sup>3</sup> Also, complex consent processes may reduce participation to the point that the study findings are no longer generalizable. Effectiveness research depends particularly on the full or nearly full participation of the study population.

Not discussed in the two papers is the important role of patients as end users of comparative effectiveness information. The Patient-Centered Outcomes Research Institute encourages comparative effectiveness researchers to fully engage patient communities in selecting and endorsing specific research questions and as participants on research teams.<sup>4</sup> With legitimate participation by the patient community, the notion of patient protection is seen in a new and distinct light—as an activity with the dual purposes of protecting against legitimate research risks and of facilitating the conduct of research requested by patients.

#### **Acknowledgments**

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# Evaluation as Part of Operations: *Reconciling the Common Rule and Continuous Improvement*

BY RICHARD PLATT, CLAUDIA GROSSMANN, AND HARRY P. SELKER

Understanding the components of clinical care that work best is a cornerstone of improving health care. And yet, the more we improve the quality of quality improvement and move to continuous learning about clinical care more broadly, the more we find ourselves in a regulatory environment that makes evaluation more difficult, expensive, and, in some situations, impossible. In their paper on the ethical underpinnings of the distinction between research and treatment, Ruth Faden and colleagues raise important implications for a wide array of situations. These points give reason to rethink the definition of routine clinical operations to include evaluation of the processes and outcomes of care and dissemination of findings.

Consider the following initiatives in response to a new commercial hand hygiene product approved by the Food and Drug Administration. Advertisements for the product claim it causes less irritation to the hands and has excellent antimicrobial properties. Hospitals interested in adopting this product might respond in different ways:

- Hospital A introduces the product. After several months it surveys the staff and reviews its patients'

rates of health care–associated infections. The minority of staff who respond report more problems with cracked skin, but whether these reports represent the experience of all staff is unclear. There were too few infections to tell if the new product made a difference.

- Hospital B's infection preventionist belongs to a professional social network and identifies fifty hospitals that have adopted the new product and fifty that have not. All the hospitals surveyed user satisfaction before and after initiation, and all are able to retrieve information about infections associated with health care. However, their user satisfaction data cannot be combined because different questions were asked. Surprisingly, the risk of new health care–associated infections appears to be *higher* in hospitals that used the new product. This unexpected result is difficult to interpret, however, because of differences in patient populations and baseline infection rates.
- Hospital C's infection preventionist identifies one hundred hospitals that are considering adopting the new product and suggests that half adopt it immediately, while the others wait. All the hospitals agree to use the same methods to monitor user satisfaction and to assess infection rates. The fifty early adopters are selected at random. This comparison shows conclusively that the new product yields better user satisfaction and a *lower* infection risk.

Do any of these examples constitute human subjects research subject to the federal policy for the protection of human subjects (the “Common Rule”) or to the research provisions of the Health Insurance Portability and Accountability Act?<sup>1</sup> Should it matter if the hospitals share their results with one another? Or with the members of a professional organization? Or in a peer-reviewed journal? Or whether a nonclinician investigator participated in the evaluation? Or proposed it? If any of these scenarios are considered human subjects research, should it be necessary to obtain informed consent from the medical staff or the visitors who use the product? From the patients who are cared for in early intervention hospitals? In hospitals that do not employ the new intervention right away? From patients whose records are retrospectively reviewed? Based on current practice, for some of these questions, the answer would be yes. But we believe this is both unnecessary and counterproductive.

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The most informative evaluation, Hospital C's, meets the standards of high-quality delivery science research, but we do not believe it should require the kind of oversight required to protect human research subjects. We concur with the assertion by Faden and colleagues (in the article on an ethics framework for learning health care systems), and with previous work from The Hastings Center,<sup>2</sup> that conducting continuous improvement activities such as these is an obligation of health systems and clinicians. We believe that rigorous, systematic evaluation should be considered part of normal, expected operations, rather than exceptional behavior that requires extraordinary regulatory control.<sup>3</sup> We also believe that collaborations between clinicians and nonclinician investigators should be encouraged, as should widespread sharing of results. Moreover, we consider institutional review board-supervised application of HIPAA safeguards that go beyond standards for treatment or operations to be unnecessary and to distract from the important concept that safeguards should be an immutable component of all health care. As described by Faden and colleagues, engagement by IRBs in this setting "is a misplaced moral moment."

Clearly, some clinical evaluations require IRB oversight. We believe oversight is necessary when an intervention carries more than minimal risk, when the intervention involves a product that is not approved for the use in question by an appropriate regulatory agency, or when the intervention is not intended to be part of regular medical practice. When none of these special conditions exists, however, then normal insti-

*We suggest a risk-based approach to the protection of participants in activities that might currently be classified as human subjects research.*

tutional systems should be used; those systems will lead to the most rapid and complete evaluation and to implementation of the highest quality care. Clinicians, medical practices, delivery systems, and health plans routinely make decisions that balance benefits against risks, or one set of benefits against another. They frequently make decisions under uncertainty. They have developed many policies, practices, and systems to oversee them, and we believe these systems are the proper ones to guide the evaluation of many aspects of care.

We suggest a risk-based approach to the protection of participants in activities that might currently be classified as human subjects research. The approach we propose is based on whether an activity is part of operations and on its level of risk for participants, as depicted in Figure 1.

In practical application, the following examples should be considered routine operations when they are intended to generate information to improve the quality of care and they do not confer more than minimal risk:

- analysis of routinely collected health care information
- analysis of administrative databases
- analyses of variations of routine care within a health care system or patient population
- surveys to assess quality and effectiveness of care
- random allocation of units of care—such as practices, hospital wards, or hospitals—to one or another approved, accepted care practice

		Risk		
		Information-only	Minimal	Greater than minimal
Motivation	Operations	institutional oversight no IRB oversight no consent needed		
	Other	IRB oversight consent requirement determined by IRB HIPAA research standards		

- collaboration of any of these activities among multiple providers or organizations
- dissemination of the results of such activities through publication or other means

In brief, we believe that rigorous, systematic evaluation of clinical practice should become the norm. Evaluation requires institutional oversight using existing mechanisms and full compliance with the privacy provisions of HIPAA that apply to treatment and operations. But evaluation of minimal-risk, approved care should not require IRB involvement, nor should it require consent from patients beyond that required for normal medical care (or from health care workers beyond the norms of employer-employee relationships). IRBs provide essential protections for patients participating in greater-than-minimal-risk research, but they can impede

progress when the risk is no greater than is typical of accepted clinical practice.

We must be able to confidently recognize better (and worse) outcomes of clinical care. The expectation and the responsibilities of health care institutions should include robust evaluation of their practice and dissemination of their findings as part of routine operations.

1. The Common Rule, “Federal Policy for the Protection of Human Research Subjects,” is based on United States Department of Health, Education, and Welfare, Code of Federal Regulations, Title 45, Part 46 (45 CFR 46), Subpart A. Identical language is used in the regulations for fifteen federal departments and agencies, which includes the creation and conduct of institutional review boards; Health Insurance Portability and Accountability Act of 1996, 42 U.S.C. sec. 1320d-9.

2. J. Lynn et al., “The Ethics of Using Quality Improvement Methods in Health Care,” *Annals of Internal Medicine* 146, no. 9 (2007): 666-73.

3. H. Selker et al., “The Common Rule and Continuous Improvement in Health Care: A Learning Health System Perspective,” October 2011, discussion paper, Institute of Medicine, Washington, D.C., <http://www.iom.edu/commonrule>.



## COMMENTARY

# Reform within the Common Rule?

BY TOM PUGLISI

In their papers in this supplement, Ruth Faden and colleagues demonstrate convincingly that the traditional distinctions between research and clinical practice—distinctions that for almost forty years have provided an ethical and regulatory framework for our current human research protection system—have become blurred from a moral perspective and outmoded from a practical perspective. They conclude that research ethics and regulation must change to accommodate a changed and changing health care environment.

The core of their argument is that the current ethical framework relies too heavily on a segregated model that uses the “research-practice distinction to identify which activities warrant ethical review and to determine when patients are at risk and in need of oversight protection.” They propose an *integrated* ethical framework that recognizes that health care institutions have a moral obligation to become learning organizations that continually improve the quality, value, and efficiency of care in support of a just health care system. The current “research risk” framework would be replaced with a “learning” framework that incorporates the rights and responsibilities of all who participate in health care activities, including patients, who within this framework have a moral obligation to contribute to a just health care system.

Although the authors offer their framework as a pragmatic solution to the confusion experienced by investigators and institutional review boards attempting to discriminate research from practice within contemporary health care systems, they

do not describe the nature and degree of oversight that would be required were their framework to be adopted. Moreover, the reality is that the widely understood and accepted risk-based ethical framework, which is founded upon the distinction between research and practice, is now and for many years has been embedded in the regulatory requirements of the Federal Policy for the Protection of Human Subjects, known as the Common Rule.<sup>1</sup> Sadly, recent proposals to modify the Common Rule have become stalled, at least for the foreseeable future, if not permanently.<sup>2</sup> Given the current political climate and the often divergent interests of the seventeen agencies that adhere to the rule,<sup>3</sup> meaningful systemic modernization of the Common Rule is not likely to occur any time soon.

All the same, modernization of the Common Rule is desperately needed. Regulatory requirements have become so complicated that most researchers cannot fully understand or remember them, and thus cannot draw the connections between many of these requirements and the goal of protecting subjects. In my experience, all but a relative handful of research investigators embrace the need to protect human subjects from reasonably foreseeable risks of harm, understand the need to protect subjects’ privacy and the confidentiality of subjects’ data, and genuinely want to comply with regulatory requirements. However, these requirements are now so detailed that they frustrate investigators (and IRB members) and undermine the respect needed to foster compliance and ensure meaningful protections for human subjects.

In addition, the IRB system has been stretched well beyond its limits. Poorly resourced and still largely dependent on the dedication of its volunteer members, IRBs are expected to do too much with too little. Regulatory requirements must be simplified so investigators can understand and respect them, and so IRBs can spend their valuable time and resources on activities that genuinely protect subjects. So how can the much-needed reform be accomplished, given current practical and political realities?

In the short term, the agencies responsible for implementation of the Common Rule—particularly the Department of Health and Human Services and its Office for Human Research Protections—must be willing to develop practical guidance for implementing the current regulatory requirements in a way that promotes clarity and understanding and allocates human and fiscal resources based on the level of risk to subjects. To this end, the Veterans Health Administration recently implemented policy to address the research-practice distinction—a distinction that is especially relevant to VHA’s

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*In the short term, the agencies responsible for implementation of the Common Rule must develop practical guidance for implementing the current regulatory requirements in a way that promotes clarity and understanding and allocates human and fiscal resources based on the level of risk to subjects.*

current challenges and that the authors of the “ethical framework” articles have identified as particularly outmoded.

From a regulatory standpoint, these authors correctly focus on the problematic definition in the Common Rule of “research”—namely, a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.<sup>4</sup> Like these authors, we in VHA have found the terms “systematic investigation,” “designed,” and “generalizable knowledge” to be inadequate for efficiently and effectively implementing Common Rule protections within what is arguably the largest integrated health care system in the United States, currently treating over six million veterans annually in 152 hospitals, 981 outpatient clinics, 133 community living centers, 98 domiciliary treatment programs, and 300 Vet Centers.<sup>5</sup>

As a learning organization, VHA conducts innumerable quality assessments, quality improvement initiatives, and system redesign projects, both across the system and within individual medical centers. Data from VHA’s massive electronic medical record system are analyzed to ensure that VHA patients receive the best care that the system can provide. These activities must be *systematic* to ensure validity and reliability, and results are often designed to be *generalizable* to the entire Veterans Affairs health care system. However, such activities are not conceived as research, are not considered research, and are not overseen as research in today’s VA. How is this possible?

VHA has adopted policy that addresses the problematic definitions in the Common Rule by clarifying how these terms are to be interpreted within the VA health care system.<sup>6</sup> The policy creates a risk-appropriate protection system that establishes accountability within the VA not only for research activities but also for what VHA defines as *nonresearch health care operations* activities.<sup>7</sup>

Operations activities may or may not constitute research, but the VHA policy identifies a substantial number of activities that typically do *not* constitute research—and thus, that do not require IRB review and oversight—when conducted within the VA health care system.<sup>8</sup> These activities include, for example, quality assessment, program evaluation, program improvement, system redesign, operational monitoring, and patient satisfaction activities designed for internal VA purposes rather than to advance the knowledge base (generalizable knowledge) of a scientific or professional discipline.

A critical aspect of the policy is that it establishes oversight accountability and documentation requirements for activities that do *not* constitute research,<sup>9</sup> and it provides a mechanism for publishing the results of such nonresearch activities (reformulating the traditional assumption, common among IRBs, that publication of results from such activities constitutes *de facto*, *post hoc* proof that the activities were prospectively designed to contribute to generalizable knowledge, and thus to have constituted research).<sup>10</sup> Specifically, VHA program office directors are accountable for system-wide, national operations activities. VHA network directors and facility directors are responsible for operations activities conducted at the network or facility levels, respectively.

Although reform of the current research oversight system through national guidance from OHRP and more limited, agency-specific guidance is itself problematic, the moral imperative for efficient and effective oversight of both research and nonresearch health care improvement activities (and other health care operations activities) demands modernization now, even if it must take place within the constraints of the current Common Rule. The two papers presented here provide a promising framework from which to begin the much-needed modernization and eventually to achieve regulatory reform.

#### **Disclaimer**

The views presented here are solely those of the author and do not represent the views of the Department of Veterans Affairs.

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2. Department of Health and Human Services, “Advance Notice of Proposed Rule Making, Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators,” *Federal Register* 76, no. 143 (2011): 44512-31.

3. The Departments of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, Housing and Urban Development, Justice, Veterans Affairs, Transportation, Homeland Security, the Consumer Product Safety Commission, the Environmental Protection Agency, the Agency for International Development, the National Aeronautics and Space Administration, the National Science Foundation, and the Central Intelligence Agency.

4. United States Department of Health, Education, and Welfare, Code of Federal Regulations, Title 45, Part 46.102(d).

5. Veterans Health Administration Office of the Assistant Deputy Under Secretary for Health for Policy and Planning, "Selected VHA Statistics: FY2011–2012," June 15, 2012.

6. Department of Veterans Affairs Veterans Health Administration Handbook 1058.05, "Operations Activities That May Constitute Research," October 28, 2011. Generalizable knowledge (sec. 4a) is clarified to mean "information that expands the knowledge base of a scientific discipline or other scholarly field of study. . . . Thus, systematic investigations designed to produce information to expand the knowledge base of a scientific discipline or other scholarly field of study constitute research."

7. *Ibid.*, sec. 4b. VA operations activities "are certain administrative, financial, legal, quality assurance, quality improvement, and public health endeavors that are necessary to support VHA's four primary missions of delivering health care to the Nation's Veterans, conducting research and development, performing medical education, and contributing to national emergency response. Operations activities may or may not constitute research."

8. *Ibid.*, sec. 5a. "Activities that are not designed to produce information that expands the knowledge base of a scientific discipline (or other scholarly field) do not constitute research. Thus, a VHA operations activity does not constitute research if both of the following criteria are satisfied: (1) The activity is designed and implemented for internal VA purposes (i.e., its findings are intended to be used by and within VA or by entities responsible for overseeing VA, such as Congress or the Office of Management and Budget); and (2) The activity is not designed to produce information that expands the knowledge base of a scientific discipline (or other scholarly field)."

9. *Ibid.*, sec. 6.

10. *Ibid.*, sec. 7.

# Advances in the Research Enterprise

BY JOEL KUPERSMITH

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The clinical research enterprise is changing in fundamental ways. The bright line that separates research and clinical care is beginning to fade as a result of new technology, methods, and thinking about the health care system. In this milieu, Ruth Faden and colleagues propose a new ethics framework for clinical research that is most timely and well considered.

Driving the change is a clinical culture focused on creating and using data to improve health care. This movement comes as we observe with more scrutiny the need to enlarge the evidence base for clinical medicine and the health care system, and the need to improve our research approaches to narrow the gap. To substantially influence this evidence gap, one needs to efficiently collect large amounts of data on routine medical care. This need fosters new types of research, such as comparative effectiveness research and methods (instrumental variables, site randomization) that examine approved treatments and are much more closely integrated with clinical care than other types of study. The Department of Veterans Affairs, for example, is piloting an approach called “Point of Care Research” that uses rigorous randomized, controlled trial methodology in a new way to compare standard clinical approaches. The trial is embedded in the VA health care system with the patient’s own physician administering the therapy and the data recorded in the patient’s electronic health record.<sup>1</sup>

Both the electronic health record and other information technology advances provide greater capacity to build large integrative databases using clinical information. In the evalu-

ation of health care systems, outside of the usual research locus, an administrative culture based on evidence has led to use of more rigorous methods in quality improvement and programmatic and other data analyses (often now mandated) that are not considered research by definition and that operate under different rules than research.

The “research” and “nonresearch” approaches converge into and are embodied by the concept of the learning health care system. Here, data about care and operations are translated into practice improvement. VA has been a leader in this area, and based on its use of electronic health records and other inputs, has formed large databases and a data-driven health care system.

These changes raise questions about the traditional approach to “research subject” protection. The research regulatory system is anchored in the definition of research as the provision of “generalizable knowledge,” according to the Common Rule. When an approach falls under this rubric, the patient becomes a research subject and a regulatory complex is triggered to maintain a bright line between research and clinical care. But that line is now in question.

For example, why are special research subject protections necessary when comparing two interventions that are both approved for clinical use—both accepted, that is, as usual care? Why should research rules apply when examining a usual care situation by rigorous means and not with methodologically less rigorous programmatic analysis or quality improvement? In fact, more rigorous approaches may be discouraged by the greater administrative burdens imposed by regulations related to research.

In this environment, Faden and colleagues directly take on the issue of formulating an ethical framework for learning health care systems based in part on interpretations of the “common good.” They suggest new standards in a construct of the learning health care system whereby certain approaches to research and learning (for example, quality improvement and comparative effectiveness research) can be grouped under learning activities and separated from research per se, but not from clinical care. They set these standards via seven obligations for both providers and patients.

In my view, there is a need to make changes in this direction, considering the large evidentiary gap in clinical care and its influence on quality. Oversight and compliance should not depend on definitions of what is or is not research, but on risk to the patient.

The interesting construct proposed by Faden and colleagues will generate much discussion about the future of research oversight. One important issue will be when and how

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*It is true that patients should be partners in learning health care systems and that patient exclusion can create bias. However, an affirmative obligation for both the patient and the provider is not ethically equivalent.*

to seek informed consent from subjects. Informed consent should be a requirement for learning activities whenever feasible. However, the complex informed consent documents now used in research should be not be required, nor are they desirable in low-risk situations. For some situations, one approach might be to obtain “blanket consents” from patients along with the usual medical consents required for clinical care—that is, broad consents that are obtained on entering the system of care that would also cover low-risk learning activities. The current policy not to require informed consent for some kinds of research—such as quality improvement and inclusion in certain databases, which may be clinically established but should be also available for learning—should be continued.

Institutional review boards have considerably expanded their role over the years. Would their approval and oversight be required for low-risk research on accepted treatments or databases? Perhaps not. Oversight could be in the clinical realm, as Faden and colleagues suggest.

Research protocol mandates—in particular, randomization and blinding—restrict the autonomy of both physician and patient. Is there risk and detriment to optimal care specifically from loss of control if the treatment is assigned randomly, and neither the physician nor the patient chooses the treatment that the patient ends up receiving? Oversight of certain randomized, “usual care” studies could be similar to the oversight of other, less rigorous learning activities. As Faden and colleagues point out, there are now also mandates in clinical protocols. In any case, explicit protocol exit strategies and flexible designs could help mitigate potential risks.

The fourth obligation in the proposed ethical framework concerns nonclinical risks. Perhaps the major nonclinical risk involves data privacy and security, especially when a person’s information is included in large databases. This risk applies not only to individuals but also to groups (for example, to statistics on mental illness in a given population). Although these risks exist with all electronically stored information, they may be greater in the context of research. Privacy laws will continue to be part of the public discussion, and it is important that appropriate sanctions should be applied for misuse.

The seventh, “affirmative” patient obligation—to participate in learning activities, and specifically for patients to join certain initiatives—raises issues of patient autonomy, even in very low or “no-risk” activities (though any activity can have unforeseen consequences). It is true that patients *should* be partners in learning health care systems and that patient exclusion can create bias. However, an affirmative obligation for both the patient and the provider is not ethically equivalent when patients, however much they have a stake in the quality of health care, are in a dependent position and shoulder any risk. Transparency, which Faden and colleagues emphasize, is certainly important, but does not solve the problem. I would favor granting more autonomy to the patient, which could be accomplished by appropriately broad or blanket consents.

One point that is perhaps implied but not made explicit in the proposed framework and that deserves to be underscored: if participating in learning activities is to be a moral obligation, those activities must be sufficiently rigorous to generate valid information. There must also be intent to translate research into clinical use, depending on the findings. Without these attributes, the effort, whatever the risk or burden, is not an ethical activity.

Faden and colleagues have taken an important forward step that is now open for debate. There are also many details to consider, such as implementation. As the head of a large research program charged with formulating and directing policies that these philosophies engender, I look forward to the discussion.

#### **Disclaimer**

The views presented here are solely those of the author and do not necessarily represent the views of the Department of Veterans Affairs.

1. L. D’Avolio et al., “Implementation of the Department of Veterans Affairs’ First Point-of-Care Clinical Trial,” *Journal of the American Medical Informatics Association* 19 (2012): e170-e176, published online February 24, 2012.

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Program, research focusing on health care and reintegration for returning veterans, development of new research approaches, and many other research innovations that have become VA landmarks.

**EMILY A. LARGENT** is a PhD candidate in Harvard University's health policy program and recently coauthored *Research Ethics Consultation: A Casebook* (Oxford, 2012). Her current research focuses on the ethics of humanitarian medicine.

**JERRY MENIKOFF** directs the federal Office for Human Research Protections and has a faculty appointment in the department of clinical bioethics at the National Institutes of Health.

**FRANKLIN G. MILLER** works in the department of bioethics at the National Institute of Health. His current research focuses on ethical issues in clinical research and end-of-life decisions.

**RICHARD PLATT** is professor and chair of the Harvard Medical School Department of Population Medicine at the Harvard Pilgrim Health Care Institute. His research focuses on developing multi-institution automated record linkage systems for use in pharmacoepidemiology, and for population based surveillance, reporting, and control of hospital-acquired and community-acquired infections.

**PETER PRONOVOST** is the director of the Armstrong Institute for Patient Safety and Quality at Johns Hopkins and Johns Hopkins Medicine's senior vice president for patient safety and quality. He is a professor of anesthesiology and critical care medicine and practicing critical care physician. He coauthored the book, *Safe Patients, Smart Hospitals: How One Doctor's Checklist Can Help Us Change Health Care from the Inside Out* (Hudson Street Press, 2010). Dr. Pronovost led the national effort that substantially reduced central-line blood stream infections across the United States and is currently leading several other national efforts to improve patient outcomes.

**TOM PUGLISI** is the chief officer and director of the Office of Research Oversight in the Department of Veterans Affairs. He is responsible for ensuring compliance in all VA research with requirements related to the protection of human subjects, laboratory animal welfare, research safety, research laboratory security, research information protection, research misconduct, and government-wide debarment for research impropriety.

**JOE V. SELBY** is the executive director of the Patient-Centered Outcomes Research Institute. A family physician, clinical epidemiologist, and health services researcher, he has more than thirty-five years of experience in patient care, research, and administration. He was elected to membership in the Institute of Medicine in 2009.

**HARRY P. SELKER** is dean of Tufts Clinical and Translational Science Institute at Tufts University and executive director for the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center. Dr. Selker has served on boards and as an officer for a variety of professional and educational organizations, including, most recently, as president of the Society for Clinical and Translational Science for 2010–2011 and as president of the Society for General Internal Medicine for 2011–2012. His research focuses on the development of treatment strategies, decision aids, and systems aimed at improving medical care, especially emergency and cardiac care, and also on methods research to advance clinical study design, mathematical predictive modeling of medical outcomes, and comparative effectiveness research.

**MILDRED Z. SOLOMON** is president and chief executive officer of The Hastings Center and clinical professor of anaesthesia at Harvard Medical School, where she directs the Department of Global Health and Social Medicine's Fellowship in Medical Ethics. Dr. Solomon is a bioethicist and social science researcher who conducts both normative and empirical research on a wide range of values questions and topics of moral uncertainty in health, health care, and public health. The primary focus of her scholarship has been on the ethics of end-of-life care for adults and children, organ transplantation, and research ethics. She is also an accomplished ethics educator and an implementation scientist who has designed and carried out numerous large-scale efforts to promote the uptake of evidence-based practice in hospitals and health systems.

**SEAN TUNIS** is the founder, president, and chief executive officer of the Center for Medical Technology Policy in Baltimore, Maryland. His work focuses on improving the quality and relevance of clinical research by providing a neutral forum for collaboration among experts, stakeholders, and decision-makers. He also advises a wide range of domestic and international public and private health care organizations on issues of comparative effectiveness, evidence-based medicine, clinical research, reimbursement, and health technology policy. Dr. Tunis formerly was the chief medical officer of the Centers for Medicaid and Medicare Services.

**DAVID WENDLER** heads the Unit on Vulnerable Populations in the Department of Bioethics at the National Institutes of Health Clinical Center. He is a philosopher trained in the philosophy of science and epistemology and has served as a consultant to numerous organizations, including the Council of International Organizations of Medical Sciences, the American College of Cardiology, and the National Institute on Aging. His current work focuses on the ethics of research with individuals who are unable to give informed consent.

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