

work at only a single hospital, which can shift loyalty away from patients and the profession and toward the hospital. Some physicians may be captured by the hospital, whose incentives to increase market share and profits are not always well aligned with the best interests of patients and communities. For example, hospital marketing may encourage patients to suppose that their relationship with the hospital is more important than their relationship with any particular physician.

And yet even hospitals suffer in some ways from the hospitalist model. As community physicians relinquish their hospital privileges, the number of physicians on hospital medical staffs tends to decline. Fewer and fewer physicians in the community ever set foot in the hospital, let alone participate in its decision making. As a result, hospital leaders can become less informed and engaged with the needs of their community. In settings where community physicians have functioned as effective

advocates, the loss of their voice can widen the gap between hospital policies and community needs.

The reality is that medicine can be practiced without hospitals, but hospitals cannot function without physicians. In war-torn parts of the world today, for example, physicians are caring for seriously ill and injured patients and even performing complex surgeries in outpatient settings.⁴ Although this state of affairs is undesirable, it's also a powerful reminder of the real *sine qua non* of medical care. A good hospital is a great boon to patient care, but the hospital itself is ultimately a tool — to be sure, a large, complex, expensive tool — without which patients can still be given care.

To position the hospital at medicine's center is to create an unbalanced system, one that will continually jar both patients and the health professionals who care for them. The true core of good medicine is not an institution but a relationship — a relationship between two human beings. And

the better those two human beings know one another, the greater the potential that their relationship will prove effective and fulfilling for both. Models of medicine that ensconce physicians more deeply in spatial and temporal silos only make the prospects for such relationships even dimmer.

Disclosure forms provided by the author are available at NEJM.org.

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This article was published on August 10, 2016, at NEJM.org.

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DOI: 10.1056/NEJMp1608289

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HISTORY OF CLINICAL TRIALS

Clinical Trials, Healthy Controls, and the Birth of the IRB

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The U.S. Office for Human Research Protections (OHRP) is revising the Common Rule that guides research involving human subjects — the first substantial overhaul of clinical research regulation in 40 years. In 2011, when the OHRP announced its plan to revise the regulations, it described the current system of review by local institutional review boards (IRBs) as burdensome for multi-site studies, such as collaborative

clinical trials, and as a force that “can significantly delay the initiation of research projects.” The revisions will have global repercussions. In determining how best to fix the Common Rule, it is important to understand how our current local review system was designed to address specific problems in the 1950s, when randomized clinical trials were first emerging.

The local IRB review model

stems from the practices that the National Institutes of Health (NIH) created for its research hospital, known as the Clinical Center, in Bethesda, Maryland. NIH scientists and lawyers created the system to manage a new kind of human subject — the “normal control” — for clinical studies that were far smaller than today's randomized, controlled trials (RCTs). Efforts to recruit healthy volunteers for medical research

created new legal and ethical dilemmas.

In the early 20th century, researchers typically enrolled healthy humans from government institutions, such as prisons and military camps, or used people they knew personally, such as medical students and family members, in research studies.¹ In keeping with this tradition, the first healthy control participants who arrived at the Clinical Center were conscientious objectors to the Korean War draft.² As the Clinical Center was set to open in 1953, NIH administrator Irving Ladimer reported that he had met with leaders of Anabaptist churches and “proposed arrangements under which I felt we could ‘purchase’ service from the organization on a man-month basis.”³ In a deal negotiated through the Selective Service System, the NIH signed contracts with two national Anabaptist churches, whose pacifist members participated in the agency’s Normal Volunteer Patient Program as a form of government-approved “alternative service.”

But the NIH immediately expanded the program to allow any member of the Anabaptist churches to participate, both so it could recruit female volunteers and to accommodate the growing number of clinical studies planned by NIH researchers. This expansion marked a crucial change in the ways in which healthy human participants could be recruited into clinical research. The NIH had created a legal, large-scale, sustainable program to recruit healthy civilians from outside state institutions who had no prior relationship with the researchers.²

This shift in recruitment, in turn, changed the agency’s approach to assessing the ethics of

research. Before the 1950s, researchers relied on informal guidelines or professional codes of ethics.⁴ When the Clinical Center opened, NIH administrators understood that recruiting healthy civilians into clinical studies in their premier federal hospital exposed the agency to new legal risks. Instead of adopting a universal set of ethical principles for researchers to interpret, the agency created a formal committee-review process to protect the federal government from legal risk in the event that a healthy civilian was inadvertently injured or killed during a study.

In 1954, the NIH set up an internal committee to review two kinds of studies conducted at the Clinical Center: the few studies that researchers believed presented an “unusual hazard” to human participants, whether sick or healthy, and any study that affected normal controls in any way. Nine of every 10 studies reviewed in the 1950s involved healthy subjects. Thus, from the outset the review system was as concerned with research involving the new kind of clinical participants — healthy civilians — as it was with studies involving sick patients.

Though the NIH had created this committee to govern intramural clinical research, administrators worried that the agency could also be held legally responsible for participants in studies that the NIH funded through its extramural program. This concern came to a head in the mid-1960s, when prosecutors approached the agency about its possible liability for a study in which an NIH-funded researcher, Chester Southam, had injected patients with live cancer cells without their consent. In

1966, to deflect potential lawsuits related to extramural studies, the NIH’s parent agency, the Public Health Service, required all institutions it funded to adopt a local review committee like that used by the Clinical Center, with the aim of making those institutions, rather than the U.S. government, liable for any ethics violations. The U.S. Surgeon General mandated this local review procedure at the recommendation of a National Advisory Health Council headed by NIH director James Shannon, who had overseen the creation of the Clinical Center’s committee-review system.

In the 1970s, revelations of horrific abuses of human subjects in the Tuskegee syphilis study — in which treatment was withheld from black men with syphilis — led to a public outcry over unethical and inhumane research practices. Various approaches to regulation were suggested. Some lawmakers, including Senator Ted Kennedy (D-MA), advocated a federal, centralized review system. But public health agencies, having used local review to deflect legal liability for publicly funded research, preferred the system they already knew. So the U.S. government standardized that model, and the 1974 National Research Act adopted a local review system for all NIH-funded sites. When human-subjects research regulations were consolidated into the Common Rule, what we now know as the IRB system was incorporated into it. Local review helped to restore trust in biomedical research by creating a decentralized system that required all institutions receiving federal funding to individually review studies involving human subjects.⁴

Yet there were hidden costs of extending local review so widely. The OHRP reports that more than 4000 IRBs are now registered, and two National Academy of Sciences panels on human-subjects research regulations have documented that the local-review requirement has created redundant work for IRBs in multisite studies. It has also fueled frustration among researchers, since different IRBs interpret the rules differently, for both good reasons (such as local context) and poorer ones (including local politics and specific pet peeves of influential members).

By revising the Common Rule, the OHRP aims to fix many of the problems that the local review system created when it was scaled up from Bethesda to research sites worldwide, even as RCTs were increasing in size and acceptability. Yet the OHRP's proposed revisions have generated at least as much controversy as they have resolved, as a recent report from the National Academy of Sciences makes clear.⁵

For example, the revisions would require most multisite, cooperative studies to use a single IRB. Under this centralized sys-

tem, either one research site would take on review responsibilities for all sites involved or research teams would all agree to use an IRB unaffiliated with any of the sites. Although this proposal is intended to streamline and accelerate review, critics worry that sites would lose the ability to adapt protocols and consent materials to their local context. The history of ethics review suggests that resistance to centralized review may stem from concern about who holds liability as well as from the desire to protect the distinct needs of specific populations. The best of the models that NIH and universities are developing for centralized review are anticipating this obstacle, but more work is needed to clarify how liability would shift.

The local review model was created to manage the ethics of clinical research undertaken at one site, on a small scale, with participants different from those enrolled in today's RCTs. Yet forms of scientific collaboration, standards of research, and political sensibilities change over time, and unfortunately, the proposed revisions include no requirement

that policymakers systematically update the regulations in the future. We may not be able to predict the new forms that medical research will take, but we can build a regulatory structure flexible enough to accommodate inevitable change — without waiting another 40 years.

Disclosure forms provided by the authors are available at NEJM.org.

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DOI: 10.1056/NEJMp1607653

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Rethinking the Primary Care Workforce — An Expanded Role for Nurses

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The adult population of the United States will soon have a different primary care experience than we've been used to. In the primary care practice of the future, the physician's role will increasingly be played by nurse practitioners (NPs). In addition, the 150 million adults with one

or more chronic conditions will receive some of their care from registered nurses (RNs) functioning as care managers.

Workforce experts agree on the growing gap between the population's demand for primary care and the number of primary care physicians available to meet that

demand. About 8000 primary care physicians (including doctors of osteopathy and international medical graduates) entered the workforce in 2015, up only slightly from 7500 in 2005. And in fact, the number of yearly entrants is expected to plateau at around 8000. But the number of primary