



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.¹ 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.² 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.³

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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,⁴ practice-based research networks,⁵ and large databases of aggregated health care claims⁶ 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.⁷

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.”⁸ As clinical research and clinical practice move closer to a deliberately integrated system, the distinction between the two is increasingly blurred,⁹ although the sharp distinction in U.S. regulations and research ethics literature

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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 1974.¹⁰ 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 populations¹¹—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.¹² 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 oversight¹³). 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.¹⁴ 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.¹⁵ 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.”¹⁶

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.”¹⁷ 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.”¹⁸ 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,”¹⁹ and, “this quest for generalizable knowledge in the service of improved health is what unites biomedical research.”²⁰

Research is described in many policy documents and in the bioethics literature as an activity *designed*—or, alternatively, *intended*—to produce generalizable knowledge.²¹ 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.²² 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*.²³ 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.²⁴ 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.²⁵

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

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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.”²⁶ While the systematic collection of data according to a predefined 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.²⁷

Most U.S. hospitals are part of the Centers for Medicare and Medicaid Services’ (CMS) Hospital Inpatient Quality Reporting program,²⁸ 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.²⁹

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.³⁰ 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.³¹ 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.³² 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.³³ 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.³⁴

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.³⁵ 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.”³⁶ By contrast, OHRP guidance states that some kinds of research with patients use “an untested clinical intervention.”³⁷ 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.³⁸ Mary Ann Bailly, 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.”³⁹

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.⁴⁰

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,⁴¹ and many surgical and diagnostic procedures diffuse into practice with little or no prior scientific study.⁴² 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.⁴³

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

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antiarrhythmic drugs for sudden death,⁴⁶ high-dose chemotherapy followed by bone marrow transplantation for breast cancer, bone cement for treatment of osteoporotic spinal fractures,⁴⁷ lung-volume reduction surgery,⁴⁸ and postmenopausal estrogen.⁴⁹ 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.⁵⁰

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.”⁵¹ Also, “women, children, the elderly, and those with common medical conditions are frequently excluded from RCTs [randomized, controlled trials],”⁵² 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.⁵³

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,⁵⁴ approximately 100,000 die from health care-related venothromboembolism,⁵⁵ 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.⁵⁶ 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.⁵⁷

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.”⁵⁸ 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.”⁵⁹

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.⁶⁰ 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.⁶¹

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.⁶² 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.⁶³ 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.⁶⁴ 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,”⁶⁵ and Michael Kottow argues that “when treatment decisions are made by protocol, the patient becomes ‘a therapeutic orphan.’”⁶⁶

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.⁶⁷ 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.⁶⁸ Formularies restrict which pharmaceuticals can be prescribed (or reimbursed), often assigning patients to generic or less expensive “first-line” medications.⁶⁹ 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.⁷⁰ 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.⁷¹ 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.⁷²

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.⁷³ 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.⁷⁴

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

We 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.⁷⁵

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.⁷⁶

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.⁷⁷ 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.⁷⁸

Overprotection is not simply a nuisance. The required oversight is costly in terms of time, human energy, and money.⁷⁹ It also results in an overburdened IRB system whose ability to provide quality oversight in situations where it is most needed is likely compromised.⁸⁰ 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.⁸¹ 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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