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The historical foundations of the research-practice distinction in bioethics

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Abstract The distinction between clinical research and clinical practice directs how we partition medicine and biomedical science. Reasons for a sharp distinction date historically to the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, especially to its analysis of the "boundaries" between research and practice in the *Belmont Report* (1978). *Belmont* presents a *segregation model* of the research-practice distinction, according to which research and practice form conceptually exclusive sets of activities and interventions. This model is still the standard in federal regulations today. However, the Commission's deliberations and conclusions about the boundaries are more complicated, nuanced, and instructive than has generally been appreciated. The National Commission did *not* conclude that practice needs no oversight comparable to the regulation of research. It debated the matter and inclined to the view that the oversight of practice needed to be upgraded, though the Commission stopped short of proposing new *regulations* for its oversight, largely for prudential political reasons.

Keywords Belmont report · Research · Practice · Innovative treatment · IRBs · History of medical ethics · Nonvalidated treatment · Politics of bioethics · Regulation · Research ethics

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Introduction

The distinction between clinical research and clinical practice dominates how we conceptualize the institutions of medicine and biomedical science. An intervention or activity is typically categorized as belonging either to clinical medicine or to clinical research. The distinction yields two purportedly distinctive domains in bioethics: medical (clinical) ethics and research ethics. The research-practice distinction similarly affects how we think about the reach of U.S. federal regulations. Research places subjects at risk and investigates unconfirmed hypotheses about treatments. Therefore, it is appropriate to regulate research. By contrast, medical practice rests on interventions of proven benefit and acceptable risk. Accordingly, practice needs no regulations comparable to those governing research.

Foundational provisions in this framework, which we will call the received view, are often attributed to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [1, sec. A, B; 2; 3, ch. 1], which was established in 1974 by the U.S. Congress and directed to "consider" the boundaries between research and accepted practice. The Commission's basic statement of the "boundaries problem" occurs in the first section of the *Belmont Report* [4]—the single most influential statement of the problem and its solution ever published. The *Belmont Report*'s conception of the research-practice distinction is still presumed in the Common Rule [5],[1] which also contains several critical terms drawn from *Belmont,* including "generalizable knowledge," "human subject," and "IRB" [5, p. 102].

In this article, we explain the rich history of debate within the Commission concerning the research-practice distinction, and we highlight the role played in the development of this account by some founders of bioethics, including Jay Katz, Robert Levine, and several commissioners of the National Commission. We start by investigating the role that Congressional hearings played in shaping the Commission's mandate. We then distinguish two phases in the Commission's deliberations about the research-practice distinction. The exploratory phase was an attempt to understand the basic moral and conceptual problems that confronted the Commission, given the public law that created the Commission. A second, resolution phase constituted the Commission's attempt to resolve the problems identified in the exploratory phase. The resolution phase eventuated in a defense of what we call a "segregation model" of the research-practice distinction, according to which research and practice form conceptually exclusive, nonoverlapping sets of activities and interventions.

However, the Commission had serious reservations about how sharply the boundaries could be drawn, largely because of problems of innovative practice and nonvalidated practice. The Commission's deliberations and conclusions about the boundaries are more complicated, nuanced, and instructive than has generally been appreciated. We will show that the National Commission did *not* conclude that

[1] In 1991 fifteen federal agencies adopted 45 CFR 46, Subpart A, which then became informally known as the Common Rule (formally "Federal Policy for the Protection of Human Research Subjects"). In 2005 technical amendments were made.

practice needs no oversight comparable to the regulation of research. It debated the matter and argued that oversight of practice needed to be upgraded, but, largely for prudential and political reasons, it stopped short of proposing regulations as the means of oversight.

The chronicle we provide has been a missing chapter in the history of bioethics until now. Some recent discussions in bioethics and health policy [6–8] make this a particularly opportune time to reexamine both the history and the central issues that history surfaces.

The origins of the National Commission and its boundaries mandate

The National Commission's work was preceded by a groundbreaking Congressional inquiry. This Congressional history is the beginning of the Commission's mandate to address the boundaries problem.

Congress expressed several concerns about research involving human subjects in the early 1970s. Senators Edward Kennedy, Jacob Javits, and Walter Mondale pushed to ensure adequate research guidelines and review. Kennedy chaired the Subcommittee on Health of the Committee on Labor and Public Welfare, where he presented an ambitious agenda of investigating health science and social policy. From February through July 1973, Kennedy scheduled hearings on human experimentation. Alleged scandals were explored and reservations about federal guidelines were offered by witnesses, including, in bioethics, Robert Veatch, Daniel Callahan, Willard Gaylin, Alexander Capron, Jay Katz, Henry Beecher, and Bernard Barber (in order of testimony) [9].

Kennedy presented some urgent issues about research and practice in his opening statement on February 21, 1973. He proposed that medical innovations should be used in clinical medicine only once they were sufficiently validated by biomedical research. He added:

> The absence of sufficient [quality] control mechanisms in the practice of medicine, coupled with the almost unlimited freedom of action which physicians have in the treatment of their patients, encourages the development of patterns of medical practice that may well be premature and based on an inadequate understanding of the new technique or new drug…. There is no malice involved in such a situation…. The question is whether or not we can tolerate a system where the individual physician is the sole determinant of the safety of an experimental procedure. [9, pp. 2–3]

Jay Katz's statements before Kennedy's subcommittee are closest to the nerve center of what would become the premier issues about boundaries [9, pp. 1049–1054, 1322–1329]. In his second testimony, when Kennedy asked him to list the most difficult and complex problems confronting what would become the National Commission, Katz responded:

> Which interactions should be designated as research and which therapy, and what are the *boundaries* between research and therapy? As you know, Senator

> Kennedy,… a physician is given a great deal of authority, a great deal of latitude in the exercise of his therapeutic functions.
>
> There is now an increasing trend to label certain studies not as experiments but as therapy because they then do not fall within the existing guidelines. We have to begin to figure out what falls within the jurisdiction of the [National] Commission. [9, p. 1328; italics added]

This statement is likely the historic source of the language used by Congress in charging the National Commission to delineate "[t]he boundaries between biomedical and behavioral research involving human subjects and the accepted and routine practice of medicine" [4]. Among the dozens of testimonies and statements in the 5 months of hearings before Kennedy's Subcommittee, no one except Katz used the language of "boundaries," and Katz presents precisely the problem about boundaries that the Senate asked the National Commission to consider. From a legislator's perspective, this boundaries mandate was meant to address two problems. The first concerned therapeutic discretion and the use of either innovative therapy or nonvalidated treatment: are physicians entitled to use treatments that are either new or not sufficiently validated, without external oversight, merely because the patient-physician relationship is a private transaction assumed to be immune from regulatory interference? The second problem was, does the absence of a clear definition of "research" create a loophole in federal guidelines that allows physician-investigators to bypass IRB review by labeling their activities "therapy" rather than "research"?

Kennedy's hearings and related forms of government scrutiny were followed by some historically noteworthy events in 1974. First, the Department of Health, Education, and Welfare (DHEW; now Department of Health and Human Services) became the first federal agency to develop publicly disclosed policies for the protection of human subjects. In May 1974, DHEW converted its grants administration policies into formal regulations [10]. Second, in July 1974, Congress passed the National Research Act with a provision to create the National Commission [11]. The National Commission held its first meeting on December 3–4, 1974, and its 43rd and final meeting on September 8, 1978. Its deliberations about the research-practice distinction unmistakably had their origins in the Kennedy hearings and the public law that created the Commission [12, pp. 12–13; 13, p. 21; 14, p. 32].

The exploratory phase

The National Commission's formal deliberations on the boundaries mandate can be dated to as early as a July 14, 1975, paper by Robert Levine, a consultant and staff member at the time. This paper was followed by an addendum dated September 24, 1975, that served as the basis for the initial discussions of the boundaries issue (between July 1975 and February 1976) [15, 16, reprinted in 17]. The evolution of the National Commission's work shows that commissioners, consultant contractors,

and staff responded to four areas deemed in need of investigation: conceptual distinctions, epistemic issues, ethical goals, and political acceptability.

Conceptual distinctions

Levine's early work on boundaries highlighted the need for careful conceptual analysis of both research and practice: "Sharp definitions of the boundaries are not required. Even a superficial exploration of this problem (contained in this paper) will reveal the impossibility of describing mutually exclusive subsets (one called research and one called practice) of the universe of activities in which health care professionals may be engaged" [15, p. 1; 17, p. 1]. Levine focused on three classes of activities that raise a boundary problem: (1) activities regarding which there is legitimate dispute over whether they constitute research or practice; (2) activities that are combinations of both research and practice; and (3) research activities that subjects are likely to misconstrue as medical practice treatments.

This approach brought to the attention of the Commission a range of problematic cases in need of clarification. Examples included innovative therapy, therapeutic research, the experimental introduction of new procedures or personnel into the healthcare system, comparisons between the safety and efficacy of two or more different treatments, and system-manipulation in which part of a healthcare system is experimentally modified with the aim of either increasing the quality of the healthcare system or its efficiency. The Commission debated each, in varying degrees of depth, during several meetings. In the end it (and Levine) would reverse the original presumption that research and practice cannot be cleanly separated. The Commission produced instead a strict segregation model. We will see that this conclusion was a compromise at the heart of the *Belmont Report*, but it was also a practical and politically astute compromise.

Epistemic issues

The Commission faced related epistemic issues, including questions about the criteria needed to distinguish between sufficient and insufficient evidence to substantiate a claim that an intervention actually produces a desired medical benefit. How do we know whether a hoped-for or claimed benefit obtains? Is scientific research the only path to the validation of a medical practice? What is the status of the many medical practices that have not been scientifically tested? Does the information that arises from observations in medical practice ever constitute an adequate evidence base for a therapeutic claim in the absence of rigorous scientific research?

A recurrent and unruly problem concerned innovative treatments and insufficiently validated treatments, including off-label use of a treatment that has been validated for some purposes. Commissioners were alarmed at the near pervasive presence in clinical care of nonvalidated or insufficiently validated treatments that fall far short of the high validation standards set by randomized clinical trials. Commissioners never specifically answered the question "under which conditions is an alleged treatment claim (or hypothesis) validated," but they were conscious that

different methods of validation are at issue in scientific research, and they were aware that not all physicians accept the view that validation is obtained only from rigorous clinical trials. They were divided as to which models were capable of reaching sufficiently validating results [14, pp. 41–42].

Much in medical practice was considered by commissioners to fall short of validation on an adequate scientific basis. This epistemic problem arose in a practical context for the Commission: the fact that a procedure or conclusion is accepted in practice by itself provides no grounds for belief that hypotheses about the safety and efficacy of a procedure are supported by sufficient evidence. Everyone practicing medicine knows this to be so, but it is indeterminate whether some of these activities constitute research or should be the subject of research studies. This problem explains why much of the National Commission's deliberations were about *inadequately supported practices and the need for research to validate or invalidate claims and practices*. However, the Commission's interest in problems of practice in the end had to yield to its central charge of determining the scope of research and the protection of research subjects.

Ethical goals

To narrow the boundaries problem to manageable dimensions, in line with the Commission's broader remit of protection of research subjects, commissioners discussed the ethical goals that the research-practice distinction was presumed to fulfill. The project of precise conceptual analysis of "research" and "practice" was regarded as instrumental to the identification of activities that, for ethical reasons, require review.

Commissioners and staff members were occasionally concerned about potential overprotection of research subjects and about the underprotection of patients. As staff member Stephen Toulmin once put it, "I suspect Congress lost its way at this point in the legislation [that presented the boundaries mandate]. I believe Congress had the idea that there was something intrinsically more risky or more hazardous about research than about normal practice, and they wished for criteria provided for recognizing that which is more intrinsically risky" [14, p. 169]. Toulmin and others hypothesized that certain medical practices, such as those based on innovative therapies, are potentially more risky than well-designed research.

In the end, however, commissioners realized that their sole responsibility was the protection of research subjects, not the protection of patients in medical practice. The risks of practice therefore faded into the background and the risks and potential benefits of research dominated the deliberations and conclusions of the Commission.

Political acceptability

Two reasons explain why commissioners shied away from a probing attempt to explore harms in and oversight mechanisms for medical practice (though this issue was deliberated, as we discuss in the next section). First, they were only asked, specifically, to investigate the ethics of research involving human subjects (as well

as how to distinguish research from practice). Second, compelling political realities influenced the National Commission's deliberations and recommendations about federal regulations. Commissioners struggled to respond to the boundaries mandate in a context that had political origins and political limits.

Commissioner Robert Cooke repeatedly pressed the case that the language of boundaries had been introduced by Congress to address problems of unsupervised innovative therapy, but he also pointed to a sensitive underlying political boundary: "There was a jurisdictional problem that if the Commission was allowed to go to the protection of human subjects in all of medicine and medical practice, then we would have been in the medical practice area, and that would have raised such a fuss in Congress and in organized medicine, that this Commission never would have been born" [18, p. 170]. Elsewhere, Cooke added that, "If there had been something [in the public law] about the investigation of practice, et cetera, it would never [have] gotten out of the committee, it would never have been passed" [14, p. 193]. These political realities left the National Commission unable to address some problems that it otherwise might have addressed—in particular, the lack of adequate oversight of forms of medical practice that use nonvalidated treatments [14, pp. 31–34].

In sum, the exploratory phase of the boundaries mandate revealed that demarcating research from practice was a complicated task and that the Commission decided that it must limit its jurisdiction to research, despite its concerns about innovative practice and the use of nonvalidated interventions. The Commission had no choice here because it had no authority to investigate practice, even when it appeared that practice was rather close to research.

The resolution phase: The segregation model's permanent embodiment in the *Belmont Report*

In February 1976, at the Smithsonian Institution's Belmont Conference Center, three successive boundaries statements were drafted by a subcommittee under the direction of Commissioner Donald Seldin [19–21]. The final boundaries statement was put aside for a year before being reexamined in February 1977 during a discussion of what would soon become the *Belmont Report*. Chairman Kenneth Ryan stated at that time that subsequent *Belmont* drafts should contain a boundaries section. The April 1, 1977, *Belmont* draft mentioned a boundaries section to be inserted *at the end* of the paper, but not until December 1977 was the February 24, 1976, boundaries statement inserted, verbatim, at the beginning of the *Belmont* text, its final resting place. Subsequent drafts of *Belmont* cut a four-page text to four short paragraphs.

The research-practice distinction

The cement of this section in *Belmont* is the segregation model of the distinction between research and practice. It had first surfaced in February 1976, when commissioners dropped the previously floated idea that it is impossible to describe "mutually exclusive subsets (one called research and one called practice)" [15, p. 1;

17, p. 1]. They affirmed that research and accepted practice do in fact form two classes of activities that are "independent, although they may coexist. They do not reside along a continuum" [19].

The National Commission thus came in *Belmont* to an elegantly streamlined segregation model that can be expressed in terms of the following five conditions (P1–P3 and R1–R2):

> "For the most part, the term 'practice' refers to interventions where":
> (P1) the purpose of an intervention is "to provide diagnosis, preventive treatment, or therapy";
> (P2) the intervention is "designed solely to enhance the well-being of an individual patient or client" (though benefit to other persons is sometimes the goal);
> (P3) the intervention has "a reasonable expectation of success."

In effect, the Commission maintains that to qualify as *practice* these three conditions must be satisfied, but it allows exceptions, which we discuss below. To qualify as *research* two conditions are central. The first is not a necessary condition for all forms of research, but the second is a necessary condition:

> (R1) there is (in pertinent research methods) a formal protocol-controlled design to test a hypothesis;
> (R2) there is an organized design "to develop or contribute to generalizable [scientific] knowledge." [4, pp. 2–3]

In the course of its conceptual analysis of "research," the Commission introduced the terminology of "generalizable knowledge" as the key condition of research (see R2). Commissioners invented this notion, and it is still today the most critical standard in federal regulations to express the difference between research and practice. It was introduced to solve problems raised by Levine's initial definition of research in terms of its aims—principally, gaining *new* knowledge—and its methods. Commissioners noticed that Levine's strategy was inadequate to distinguish the type of knowledge generated in research from the patient-specific knowledge gained through medical diagnosis and treatment. The Commission's final boundaries statement in *Belmont* claimed that the requirement of generalizability handled this concern [14, p. 198]. The proposal was that knowledge gained through research must be oriented toward the type of generalizations found in scientific theories, scientific laws, and statements of relationships, in contrast to learning that occurs in particular cases through astute clinical observations or by means of diagnostic tests.

The criterion of generalizable knowledge, once articulated, did not generate any substantial debate among commissioners as to its meaning or its ultimate adequacy with regard to various types of learning activities. The notion was not then, and has never since been, carefully analyzed in Commission deliberations, in federal regulations, or in the bioethics literature. This fact is striking inasmuch as generalizable knowledge is the cornerstone of the work of the National Commission and in federal regulations for the purpose of distinguishing research from practice. Nothing is more basic.

The segregation model constituted by P1–P3 and R1–R2 above serves as the Commission's principal basis for determining which "activities ought to undergo review for the protection of human subjects of research." In the concluding sentences of the boundaries section in *Belmont*, an extension of this norm is recommended: "it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project…. The general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects" [4, pp. 2, 4]. This provision is intended to solve the problem raised by investigators who take advantage of a loophole in the oversight system and label activities involving a research component "practice" in order to avoid IRB review.

The fact that the Commission singles out "major innovations" is no indication that commissioners believed that medical practice was not in need of upgraded forms of oversight. Commissioners were merely reluctant to support regulatory oversight for the political reasons previously highlighted: their mandate did not extend to medical practice, and organized medicine would have opposed, and likely squashed, any attempt to regulate practice. The boundaries statement and early drafts of *Belmont* contain a passage asserting that "committee[s] whose responsibility is to review practice of the discipline involved" (such as hospital boards, tissue or medical practice committees, professional societies, and Professional Standard Review Organizations) have a "duty … to develop mechanisms for the systematic appraisal of [insufficiently validated] techniques and procedures in current practice" [21, p. 4]. This statement was deleted from the distilled and cleansed boundaries section of *Belmont*, but it would be reiterated and supported in a limited way in the Commission's later published volume *Ethical Guidelines for the Delivery of Health Services by DHEW* (a report and set of recommendations on the appropriateness of applying certain guidelines developed for research to the delivery of services to patients under programs conducted or supported by the DHEW) [22, pp. 104–105]. It was the only part of the Commission's mandate that touched on medical practice in areas explicitly under the purview of the federal government. The Commission never abandoned its conviction that medical practice needs robust oversight mechanisms.

The Commission's persistent doubts about its account of practice

Despite the bare-bones conditions that delineate the segregation model in *Belmont*, commissioners and staff appreciated that the definition of *practice* is far messier than *Belmont* could be expected to explore. The commissioners' wariness about how to express this untidiness was present as late as the 40th meeting in March 1978, when commissioners and staff were busy finalizing the *Belmont Report*. A major problem they saw in the medical area (we here set aside the Commission's thoughts about the behavioral and social sciences, and related areas) concerned activities such as vaccination, blood donation, organ transplants, and the use of tranquilizers on the mentally ill in medical institutions. Levine labeled the problem raised by these examples as "practice for the benefit of others" [22, p. 54]. These cases threatened the Commission's account of "practice" as fundamentally an activity

purely for the benefit of individual patients. Commissioners concluded that such a definition did not provide an adequate set of conditions of "practice."

Unable to substantially revise the definition of "practice" and unwilling to venture yet again into what commissioners categorized as the "philosophy of practice," commissioners and staff reasoned that the logical incompatibility between practice for the benefit of others and practice as an activity *solely* designed to enhance the well-being of particular patients could be eliminated by some fairly simple qualifications. The solution was to restrict the scope of practice to *paradigmatic* cases of medical practice involving individual patients and physicians, leaving the scope of nonparadigmatic practice (where all the subtleties and difficulties lay) largely unexplored in *Belmont*.

The *Belmont* draft of April 6, 1978, was then crafted to read, "*For the most part*, practice involves interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success" [23, p. 2; emphasis added]. This wording, absent from all earlier drafts, thereafter became a permanent provision in *Belmont*. A qualifying footnote was introduced stating that practice "usually" involves interventions solely to benefit an individual patient. The point of these qualifications was to reassure readers that activities partly or in whole designed to benefit others do not threaten the research-practice distinction as the Commission had developed it. Whether activities such as blood donation are practice or not, they are not research because they do not aim at generalizable knowledge. Even though the concept of practice was viewed as a byzantine morass, commissioners reasoned that their primary goal was to provide IRBs with a clear definition of research that would allow them to identify what they needed to review [24, pp. 15–33].

Commissioners thought they had done enough for purposes of public policy by distinguishing research from practice, whatever those various forms of practice might turn out to be on a closer inspection of the scope of practice. This perspective again shows the enormous importance of the criterion of generalizable knowledge. Despite the Commission's failure to provide an illuminating analysis of this concept, it is the foundation stone of the Commission's conceptual and moral scheme in *Belmont* and beyond.

Conclusion

Various strands in this paper that explore what the National Commission did *not* conclude in its embrace of the segregation model, can now be pulled together. First, it did not conclude that research is riskier than practice or that patients in medical practice are not vulnerable in ways comparable to vulnerable subjects in research. It concluded only that these matters were beyond the Commission's assignment to delineate boundaries. Second, it did not reach the conclusion that practice needs no regulation comparable to the regulation of research. It debated this matter, but remained agnostic about it in *Belmont*. Third, the Commission did not conclude that clinical practice is logically defined by interventions designed solely for the benefit of individual subjects. Its precise conclusion was only that "for the most part"

practice refers to this form of intervention. Fourth, it did not conclude that research and practice cannot be "carried on together when research is designed to evaluate the safety and efficacy of a therapy" [4, p. 4]. It affirmed that they can be so integrated. Its segregation thesis is merely that research interventions are logically distinguishable from practice interventions. *Belmont* claimed no more than that an activity involving both research and practice components must be reviewed as research even if its primary goal is improving treatment for patients. The Commission used its mandate to protect subjects by broadly envisaging the activities that fall under "research."

These conclusions are important if for no reason other than that *Belmont* and federal regulations have so often been interpreted otherwise.

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