

# The Line Between Clinical Innovation and Human Experimentation

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## I. THERE IS NO LINE

Research ethics scholars and oversight entities already know that drawing a line between human experimentation and medical treatment is surprisingly difficult, not only for patients but also for physicians.<sup>1</sup> Innovation, which is not exactly research and not exactly treatment either, overlaps both ends of whatever line—however fuzzy—there might be, making distinctions even more difficult.<sup>2</sup> The *Belmont Report*<sup>3</sup> provides definitions of all three of these key terms.

First, the Belmont Report defines medical practice as “interventions that are designed solely to enhance the well being of an individual . . . and that have a reasonable expectation of success.”<sup>4</sup> Next, it defines research as “an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge . . . .”<sup>5</sup> Finally, the Belmont Report distinguishes innovation from research: “The fact that a procedure is . . . new, untested or different does not automatically place it in the

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<sup>1</sup> “Patients . . . did not readily make distinctions between research and medical treatment. Particularly for patients with serious medical diagnoses, research was viewed as one of the treatment options for their medical conditions.” ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT (1995). “The line between treatment and research is not always clear to clinicians.” GAO, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS (1996).

<sup>2</sup> See Nancy M. P. King, *Experimental Treatment: Oxymoron or Aspiration?*, 25 HASTINGS CTR. REP. 6 (July/Aug. 1995); see also Nancy M. P. King & Gail E. Henderson, *Treatments of Last Resort: Informed Consent and the Diffusion of New Technology*, 42 MERCER L. REV. 1007 (1991).

<sup>3</sup> NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, DHEW Pub. No. (OS) 78-0012 (1978) [hereinafter BELMONT REPORT], available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>.

<sup>4</sup> *Id.*

<sup>5</sup> *Id.*

category of research. Radically new procedures . . . should . . . be made the object of formal research at an early stage in order to determine whether they are safe and effective.”<sup>6</sup>

Briefly, then, how does innovation differ from standard medical practice? By virtue of its novelty, it lacks a reasonable expectation of success. And how does it differ from research? By virtue of its individualized focus, it lacks the theoretical and empirical preclinical groundwork that characterizes the search for knowledge generalizable beyond an individual patient. Unlike research, innovation always involves sick patients. All sick patients are a vulnerable population to at least some degree, and innovation is quite likely to involve desperately sick patients, who may be especially vulnerable because they are regarded as having little or nothing to lose. As a result, innovation necessarily involves the maximum tolerable amount of uncertainty, and often what I have come to call “desperation creep,” the inevitable, heartfelt, disturbing—and ever-expanding—argument that taking time to move forward with some care simply sacrifices desperate patients to the insensitive demands of science.

Innovation in medicine is historically regarded as both common and exciting. The chances are high that each of us has a romantic image of the daring improviser—most probably a surgeon, or a trauma physician with an unpopular idea, but perhaps also a brilliant scientist, driven by the illness of someone close to play an unprecedented and winning hunch. In this context, measured scientific progress often is painted not as prudent but as dangerously pedantic. Surgical innovation is the norm rather than the exception, in part for historical and cultural reasons—that is, surgery is in some respects different from the rest of medicine—and in part because technical innovation is closely related to the improvisation that is expected when surgeons must address the unique anatomy of an individual patient.<sup>7</sup> Yet the history of medicine is full of examples of medical innovators from all specialties, and popular culture likewise abounds with images of the physician-scientist as Lone Ranger.<sup>8</sup>

The innovator’s intention is to benefit the patient. The novelty

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<sup>6</sup> *Id.*

<sup>7</sup> See, e.g., David A. Grimes, *Technology Follies: The Uncritical Acceptance of Medical Innovation*, 269 JAMA 3030 (1993). In addition, see the many surgical examples given in JAY KATZ ET AL., *EXPERIMENTATION WITH HUMAN BEINGS* (1972).

<sup>8</sup> Even the FDA “treads lightly upon the practice of medicine and surgery,” thus implicitly encouraging this overwhelmingly positive view of unregulated innovation. Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 392 (1996).

of the proposal and the confidence of the innovator combine to produce both optimism and the expectation of success—usually in the absence of much supporting evidence. When the circumstances call for drastic measures, there seems to be nothing to lose from a leap into the unknown. And then, apparently promising innovations, piloted out of necessity and lack of information, easily become standardized by virtue of enthusiasm and by default. Scholars like John McKinlay and Thomas Chalmers recognized this in classic writings now twenty and twenty-five years old.<sup>9</sup> Despite recognition of this trend, it continues largely unexamined, and may even be accelerating, a result of the changing role of the media in promotion of medical innovation. For example, the New York Times recently reported as a major story one instance of in utero repair of a fetal heart valve defect that causes hypoplastic left heart syndrome.<sup>10</sup> Undoubtedly, others will attempt the same procedure—but probably not in a clinical trial.<sup>11</sup>

Modern reality can of course differ greatly from romantic images of innovation. Physician-innovators may be known and valued for their ability and willingness to push the envelope and capture both attention and financial support in practice areas that have been historically exempted from standardized research pathways—specialties such as surgery, emergency and trauma medicine, and brain and spinal cord injury and rehabilitation.<sup>12</sup> Most interestingly, although many innovations emerging from these areas may not be routinely subjected to testing in clinical trials, they are often routinely paid for by patients' health insurance, and may even be patented.<sup>13</sup> Thus, our fascination with innovation is frequently both prestigious and lucrative for major medical centers, and innovative practitioners are sought-after and valued as teachers, mentors, and faculty stars. Since medical innovators are, in the modern era, expected to produce not only cures but also products, the outcomes of innovation are expected to be generalizable—by a path that differs significantly from the trajectory of clinical research, but that at least suggests the desirability of comparable oversight.<sup>14</sup>

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<sup>9</sup> See King & Henderson, *supra* note 2.

<sup>10</sup> Denise Grady, *Operation on Fetus's Heart Valve Called a "Science Fiction" Success*, N.Y. TIMES, Feb. 25, 2002, at A1.

<sup>11</sup> See also the examples discussed in King, *supra* note 2, and King & Henderson, *supra* note 2.

<sup>12</sup> Sandra Blakeslee, *Therapies Push Injured Brains and Spinal Cords Into New Paths*, N.Y. TIMES, Aug. 28, 2001, at F6.

<sup>13</sup> See discussion in King, *supra* note 2.

<sup>14</sup> The 1996 "emergency waiver" rule, whereby in clinical trials under specific

## II. OVERSIGHT

Should oversight be *post hoc*, through common law malpractice litigation requiring a showing of harm and triggered by the injured party, as for medical practice? The history of science demonstrates an evolving understanding of the relationship between innovation and standard treatment.<sup>15</sup> In early common law, standards of strict liability were applied to any deviation from accepted practice.<sup>16</sup> These standards were recognized as discouraging medical progress, but only the development of an organized system of clinical research succeeded in relaxing strict liability.<sup>17</sup> Since innovation is not research, it is unclear whether *post hoc* review through civil litigation constitutes adequate oversight.<sup>18</sup> Perhaps there is an intermediate option, or more than one, involving intraprofessional peer review and consent guidelines, at the level of a division, department, institution, or professional association.

A key question about the timing and nature of oversight of innovation is often posed as one of individual choice versus advance control.<sup>19</sup> Evidence that enthusiasm for new scientific possibility can get ahead of what is best and safest is provided by recent scholarly and media discussion of living donor liver lobe transplantation, which has proven unexpectedly risky in adults as compared with children.<sup>20</sup>

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circumstances the consent of subjects and their legally authorized representatives to research participation is waived, could be described as one attempt to systematically study innovations in emergent care, using the existing oversight system. See DHHS, Waiver of Informed Consent Requirements in Certain Emergency Research, 61 Fed. Reg. 51531 (1996). In fact, however, it was sought by FDA, to facilitate testing of new products under its jurisdiction, such as artificial blood substitutes, and adopted by DHHS in the interests of harmonization. It is highly controversial—for reasons not related to innovation *per se*—and has not been widely used. See generally Case 6, in BEYOND REGULATIONS: ETHICS IN HUMAN SUBJECTS RESEARCH (Nancy M. P. King et al. eds., 1999) [hereinafter BEYOND REGULATIONS].

<sup>15</sup> See, e.g., HARRY M. MARKS, THE PROGRESS OF EXPERIMENT: SCIENCE AND THERAPEUTIC REFORM IN THE UNITED STATES, 1900-1990 (1997).

<sup>16</sup> See generally Slater v. Baker, 95 Eng. Rep. 860 (K.B. 1767); Carpenter v. Blake, 60 Barb. 488 (1871).

<sup>17</sup> Brown v. Hughes, 30 P.2d 259, 263 (Colo. 1934); see also Fortner v. Koch, 261 N.W. 762, 765 (Mich. 1935).

<sup>18</sup> This issue was contested in papers commissioned for the *Belmont Report*. See Robert J. Levine, *The Boundaries between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine* (1979), in BELMONT REPORT, *supra* note 3, app. vol. 1, at 1-37; see also John Robertson, *Legal Implications of the Boundaries Between Biomedical Research Involving Human Subjects and the Accepted or Routine Practice of Medicine* (1979), in BELMONT REPORT, *supra* note 3, app. vol. 1, at 16; King, *supra* note 2.

<sup>19</sup> This is how John Robertson framed the issue in his paper commissioned for the *Belmont Report*. See Robertson, *supra* note 18.

<sup>20</sup> David C. Cronin et al., *Transplantation of Liver Grafts from Living Donors into*

Yet the alternative, as Henk ten Have has noted, is poorly addressed in public discourse about the assessment of new technologies: we simply do not seem to know how to get ahead of the science in a way that is meaningful for policy, ethics, or law.<sup>21</sup> So we end up swinging on an endless pendulum, from excessive promotion of the promising to overinclusive prohibitions and controls after someone has died—with little sense of the need to find a point of balance in between.<sup>22</sup>

Thinking about innovation thus entails thinking about ways of negotiating between choice and control. One way in between is the “*n* of 1 experiment,” such as that described by Jerome Groopman in one of his *New Yorker* columns a few years ago.<sup>23</sup> It is the story of a surgeon whose colleagues united to help him devise an individually tailored innovative intervention for his cancer. While few have the scientific or financial resources to follow Dr. Fair’s lead, some scholars have argued that the genetic revolution portends exactly this sort of individually tailored research and treatment.<sup>24</sup> But others, notably pediatric palliative care expert Dr. Joel Frader, have long argued that traditional patterns of innovation make good data-gathering difficult and adequate informing of patients impossible.<sup>25</sup> Frader’s examples include novel methods of treating respiratory failure in newborns; surgery and transplant for hypoplastic left heart; and approaches to short bowel syndrome (a complication of prematurity), ranging from aggressive parenteral nutrition to bowel transplantation. Frader notes that some innovations can have unexpected and severe side effects; that innovations are subject to bias, fashion, and other influences; and that trials comparing competing innovations are rarely undertaken. He argues that comparative trials have the capacity to address quality of life issues, economic costs, and psychosocial costs in addition to more conventional criteria such as morbidity and mortality. He further

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*Adults—Too Much, Too Soon*, 344 *NEW ENG. J. MED.* 1633 (2001); Denise Grady, *Liver Donors Face Perils Known and Unknown*, *N.Y. TIMES*, Mar. 19, 2002 at F1.

<sup>21</sup> Henk ten Have, *Medical Technology Assessment and Ethics: Ambivalent Relations*, 25(5) *HASTINGS CTR. REP.* 13 (1995).

<sup>22</sup> Anna Mastroianni & Jeffrey Kahn, *Swinging on the Pendulum*, 31(3) *HASTINGS CTR. REP.* 21 (2001).

<sup>23</sup> Jerome Groopman, *Dr. Fair’s Tumor*, *THE NEW YORKER*, Oct. 26, 1998, at 78.

<sup>24</sup> See, e.g., Noguchi, *supra* note 8 at 372 (“We are on the verge of a true medical revolution of patient centered therapies. Patients will become the focus of therapeutic strategies in which each patient represents a unique, but treatable, spectrum of disease and disability.”).

<sup>25</sup> Portions of Frader’s argument appear in *SEMINARS IN PEDIATRIC SURGERY* (2001), and in Laurence B. McCullough et al., *SURGICAL ETHICS* (1998), but the more complete elaboration described here is from an unpublished lecture.

notes that the results of such trials have the potential to greatly assist both families and policymakers in choosing among alternative interventions.

### III. DECISIONMAKING

Good information is critical to good decisions. For some time it has been recognized that the informed consent process “encourages self-scrutiny by physician-investigators” by requiring them to make their reasoning, and the evidence upon which it is based, transparent to patients and subjects.<sup>26</sup> Innovations, whose goal is benefiting the individual patient, must be talked about in ways that make the hoped-for benefit clear, and at least minimally assess its likelihood, even when there seems to be “nothing to lose.”<sup>27</sup> Thus, both the extent and nature of the evidence about potential benefit from an innovation, and the interpretation of that evidence under the circumstances, must be considered.

Essentially by definition, data about innovations are lacking. Generally speaking, data do exist to justify standard practices, though such data may be scant, depending on both the intervention and the disease. Lack of experience, by contrast, is particular to individuals and institutions, and can be a complicating factor for both innovation and practice.<sup>28</sup> Also complicating the data is the truism that there is uncertainty about the risks of harm and the potential for benefit for every individual application of any medical intervention or technology. This truism means little more than that regardless of probabilities, two things are true for every individual receiving any medical, research, or innovative intervention: something unexpected can always happen; and for each individual, any outcome, good or bad, will either materialize or not.

Of course, the probabilities and their meaning are distinctive for innovations, which are often tried in patients for whom standard treatments have a low likelihood of success, and for whom the burdens of disease are high. The key policy question, then, comes when the desperate patient (or family member) seeks the right to try a last-resort innovation. When there are few data, the innovative practitioner lacks experience, and the potential benefits seem much

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<sup>26</sup> Alexander M. Capron, *Informed Consent in Catastrophic Disease Research and Treatment*, 123 U. PA. L. REV. 340, 371-73 (1974).

<sup>27</sup> Nancy M. P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332, 335 (2000) [hereinafter King, *Defining and Describing*].

<sup>28</sup> See, e.g., Atul Gawande, *The Learning Curve*, THE NEW YORKER, Jan. 28, 2002, at 52.

slighter than the potential harms, but the burdens of disease seem to outweigh those harms, is there any innovation that can fairly be called unreasonable? Consider the example of an innovative treatment for a uniformly fatal disease. Imagine that standard treatment for the disease has a less than twenty percent chance of producing a durable (5-year) remission, and that it also offers a great deal of inevitable morbidity in both the short term and the long term, with a ten- to twenty-percent likelihood of death from treatment. An innovation with an entirely new mechanism of potential effect against the disease is proposed, with little information available about potential harms or the likelihood of any benefit. Is trying anything new “reasonable” against that backdrop? I think not; yet we have no organized way of addressing what a reasonable expectation of success should mean.<sup>29</sup>

Facing the prospect of making the difficult determination that some innovations should not reasonably be offered suggests that the drive toward innovation and medical progress should be governed by standard principles about the use of new interventions in humans. The system of research oversight, imperfect as it is, does a respectable job of devising, justifying, and enforcing just such standards for safety, disclosure, and decisionmaking about new interventions. Thus, ultimately I believe that innovation should be treated more like research than like treatment. Innovation and research share the multiple uncertainties already mentioned—lack of data, lack of experience, and often, significant imbalances between benefits and burdens. But since preclinical research is normally required to justify moving to research with humans, there may often be more uncertainty in innovation than in research, and even significant innovation could in theory be quite unprecedented, supported not by data but by reasoning and intuition alone.

One potentially great difference between treatment and innovation lies in what it means to be a subject. Being a research subject has a specific meaning beyond receiving an experimental intervention: it means being someone who is valued for providing

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<sup>29</sup> The best description I know of addressing when a research intervention may be offered as potentially beneficial states that “the possibility of benefit to the subject must be fairly immediate [and t]he expectation of success should be well-founded scientifically . . . .” NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, RESEARCH INVOLVING THOSE INSTITUTIONALIZED AS MENTALLY INFIRM 31 (1978), *quoted in* 1 NBAC, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY 44 (1998). Yet it contains far too many vague and disputable key terms to set a clear and reproducible standard. *See generally* King, *Defining and Describing*, *supra* note 27.

information. Research subjects undergo scrutiny and testing beyond that which is needed for their own well-being, so that investigators can determine how best to help future patients. Even their candidacy for an intervention is driven at least in part by their capacity to contribute to generalizable knowledge. In contrast, patients who are recipients of innovation need only be capable of benefiting if the innovation is successful; yet that is precisely what is most difficult to predict when uncertainty is greatest and the available evidence is scanty. How, then, can decisions be made by physicians and patients about what to do next in unprecedented circumstances?

Let us go back to the basics of informed consent.<sup>30</sup> Informed consent in practice settings is highly variable, honed as it is not only in the “laboratories” of state common and statutory law but also in the practices of individual healthcare institutions and the departments, divisions, and services within those institutions, as well as in professional and specialty society guidelines and almost innumerable other ways. Anything approaching the standardization, however imperfect, that is offered by the federal Common Rule governing human subjects research<sup>31</sup> is pretty much nonexistent on the practice side, even though the list of disclosure elements—nature, consequences, risks, benefits, alternatives—is quite similar. Physicians still largely learn the informed consent process through the highly informal mentoring method of “see one, do one, teach one”—though in a few areas, such as end-of-life decisionmaking and intensive care settings, concerted efforts at standardization, teaching, and process improvement are underway.<sup>32</sup>

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<sup>30</sup> RUTH R. FADEN ET AL., *A HISTORY AND THEORY OF INFORMED CONSENT* (1986).

<sup>31</sup> The Common Rule is the shorthand name for the set of federal regulations governing federally funded research with human subjects, which implement the National Research Act of 1974, Pub. L. 93-348 (1974). The regulations from seventeen federal departments and agencies were harmonized into the Common Rule in 1991, *see* 56 Fed. Reg. 28,012 (June 18, 1991), and are codified separately for each signatory body.

<sup>32</sup> One example is neonatology. A neonatologist with whom I teach was asked by her division chief to “write some informed consent policy” to alleviate confusion about what procedures and interventions did and did not require consent forms with parental signatures. The problem arose because everyone knows that you need signed consent forms for the OR, but many invasive procedures on ill neonates now take place in the NICU, so the traditional written/oral consent line was becoming blurred. Innovation was blurring the line too, because some things were unprecedented but were not “research.”

Instead of drafting policy, my colleague wrote a guidance document dividing interventions into three decisionmaking categories. Category I, a formalized requirement for a signed consent form, was limited to interventions covered by state law or hospital policy. Category II covered situations in which a significant conversation with parents was indicated, focusing on the goals, expected benefits,

In my view, comprehensive conceptual analysis and beginning standardization of decisionmaking in particular practice areas is not only necessary, but actually possible. Such analysis and standardization are important underpinnings of a goal-focused decisionmaking process, as the advance care planning literature shows, and the same information is critical to goal-focused decisionmaking about all interventions, whether they are categorizable as research, innovation, or standard practice. What really matters to individual decisionmakers are their expectations about benefits, and whether there is evidence in support of those expectations.

#### CONCLUSION

Does clinical innovation need more oversight? Yes. Should this oversight fall to IRBs? Maybe. Sometimes.

Although I think a great deal of substantive innovation is not just *like* research, it *is* research, I will still say “not necessarily.” Sometimes the hard question is really how substantive an innovation is. Medicine is as much art as formula, and innovation is a necessary component of medical thinking. And finally, IRBs already have plenty to do.

Nonetheless, for most if not all proposed innovations, the IRB’s model of setting forth guidance and engaging in prior review makes sense to me. So does the IRB’s model of determining that sometimes, prior review is unnecessary, but even then, careful disclosure, discussion, and decisionmaking are essential.

Finally, this examination of innovation also demonstrates the need for closer and more systematic attention to informed consent and decisionmaking on the practice side. The mere invocation of intent to benefit a patient is not sufficient by itself to justify any intervention, however categorized. Once this is recognized, it

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and potential risks of recommended treatment, and encouraging parental participation in decisionmaking—for example, non-emergency interventions with unclear harm/benefit ratios, or interventions about which parents are known or likely to have views or values that should be addressed. Discussions and decisions in this category were to be documented reasonably thoroughly in the infant’s medical record. Finally, Category III covered most routine NICU care, and focused on ongoing discussion of the infant’s condition and treatment, either before or after particular interventions, with checkbox or simple documentation considered sufficient. The idea behind this category was that most of the time, the shared goals of parents and team for an infant are clear, and ongoing routine discussion establishes a decision-making relationship that provides parental education and support, offers involvement, and seeks agreement, while also laying groundwork for tougher decisions and potential disagreements should they arise.

becomes clear that consent-related discussion of the nature, magnitude, and likelihood of benefit, from both standard treatment and innovative treatment, is very often insufficient.<sup>33</sup>

There are many possible forms of oversight that could be crafted from existing professional and institutional teaching and regulatory structures. Prior review of substantive innovations, including development and use of guidelines, guidances, and policies, can supplement *post-hoc* mechanisms like tort law. Standardization of the two essential components of decisionmaking—“Is this innovation ready to offer?” and “Has enough information been provided to support the offer’s acceptance?”—could be accomplished simply by requiring the physician innovator to provide a reasoned justification,<sup>34</sup> to patients and, in some cases, also to peers, for a proposed innovation. Extensive collegial teaching and modeling of responsible innovation and informed consent practice would also be helpful. Unfortunately, in the current fiscal climate, time for such teaching is in increasingly short supply. Yet as the pace of change continues to quicken in medicine, even modestly increased oversight could do much to ensure that innovation is reasonably safe, thoughtfully undertaken, and fair to patients.

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<sup>33</sup> Yet negligence law has proven spotty and inefficient at improving informed consent practice, as well as at reminding us that consent, while necessary, is insufficient to justify any and all innovation. See King, *supra* note 2. After all, even when sick patients are research subjects, physician-investigators routinely claim—and sincerely believe, even in the case of phase I dose-finding safety/toxicity trials—that benefit is possible, and sought, for each individual subject. See King, *Defining and Describing*, *supra* note 24, and citations therein.

<sup>34</sup> See King, *supra* note 2.