

## PROTECTION OF HUMAN SUBJECTS: IS EXPANSIVE REGULATION COUNTER- PRODUCTIVE?

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### INTRODUCTION

Recently, there has been renewed tension between those who doubt the wisdom or propriety of further regulating scientific research and those who believe that research, whether federally funded or not, is no different than any other commercial activity and, therefore, may be freely regulated by the federal government or the states. This tension is evident in the recent debate over stem cell research where the federal government has refused to fund most such research.<sup>1</sup> It is also evident in the ongoing debates over the extent to which the federal government ought to regulate research involving human subjects where the government has for nearly three decades imposed a detailed system of prophylactic regulation.<sup>2</sup>

Under current law, proposed research of virtually any type<sup>3</sup> that involves human subjects and is either federally funded or within the jurisdiction of the Food and Drug Administration (“FDA”) must be reviewed, analyzed, debated, and approved by an institutional review board (“IRB”).<sup>4</sup> Many argue that this IRB-based system for protecting human subjects is

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<sup>1</sup> Compare The American Association of the Advancement of Science, Scientific Freedom, Responsibility and Law, <http://www.aaas.org/spp/sfrl/projects/stem/index.shtml> (last visited Oct. 15, 2006), with President Discusses Stem Cell Research, <http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html> (last visited Oct. 15, 2006).

<sup>2</sup> See 45 C.F.R. pt. 46 (2006); 21 C.F.R. pts. 50, 56 (2006).

<sup>3</sup> The regulatory system does not apply to certain types of research including, by way of example, educational testing research (for example, the College Board evaluating questions for a future LSAT as part of a current examination), observations of elected or appointed government officials, and studies of consumer preferences for various foods. See 45 C.F.R. § 46.101(b) (2000).

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

necessary to protect those who volunteer as subjects and that such review actually promotes the ability of researchers to recruit volunteers.<sup>5</sup> Advocates of continued or expanded regulation note that biomedical research is inherently dangerous, a fact highlighted by the widely reported deaths of research subjects at the National Institutes of Health, the University of Pennsylvania, Johns Hopkins University, and St. Elizabeth Medical Center in Boston.<sup>6</sup> These advocates go on to note that most subjects do not fully appreciate these inherent risks and that IRBs protect them by ensuring that the benefits of the proposed research outweigh its risks and that the informed consent form that each subject reads and signs accurately portrays the attendant risks in language that can be understood by the average lay person.<sup>7</sup>

Others, however, argue that, while the IRB system may be appropriate for biomedical research, it is overkill when applied to social science research and also raises significant First Amendment issues. Most social science research involves human observation or paper-and-pencil testing. As such, some have argued that social science research is more speech-oriented than conduct-oriented and, therefore, the review and approval requirements inherent in the IRB system are nothing more than improper prior restraints that promote conformity and stifle creativity.<sup>8</sup> More pragmatically, many, including myself, believe that the IRB system serves little useful purpose when applied to social science research. There have been no reported deaths involving social science research and the risks associated with such research, aside from paper cuts, tend to be *de minimis*. Some have argued that continuing to impose IRB requirements on social science research may actually imperil subjects by diverting resources from areas where there are real risks to subjects' health—i.e., biomedical research.

After presenting a brief history and summary of the existing regulatory framework, this article highlights a series of emerging regulatory issues. First, it examines recent attempts to extend the current regulatory regime to non-federally funded, non-FDA regulated research involving human subjects, and questions whether these attempts make sense, both as a matter of public policy and in light of the Commerce Clause issues they may raise.

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<sup>5</sup> See Office for Human Research Protections, <http://www.hhs.gov/ohrp/about/ohrpfactsheet.pdf>.

<sup>6</sup> See *Darke v. Estate of Isner*, 20 Mass. L. Rptr. 419, 2005 WL 3729113 (Mass. Supp. 2005); L.C. BECKER ET AL., REPORT OF INTERNAL INVESTIGATION INTO THE DEATH OF A VOLUNTEER RESEARCH SUBJECT (Johns Hopkins University Report, July 16, 2001), available at [http://www.hopkinsmedicine.org/press/2001/July/report\\_of\\_internal\\_investigation.htm](http://www.hopkinsmedicine.org/press/2001/July/report_of_internal_investigation.htm); M. Milford, *Lawsuits Attack Medical Trials*, 23 THE NAT'L L.J., Aug. 27, 2001, at A1; J. Washburn, *Informed Consent*, WASH. POST, Dec. 30, 2001, at W16; see also *Grimes v. Kennedy Krieger Inst.*, 782 A.2d 807, 856 (Md. 2001) (environmental research funded by the EPA); Philip J. Hiltz, *A Second Death Linked to Gene Therapy*, N.Y. TIMES, May 4, 2000, at A-20. One of the early instances of a death in an apparently healthy volunteer occurred at the National Institutes of Health in 1980. See Gina B. Kolata, *NIH Shaken by Death of Research Volunteer*, 209 SCIENCE 475, 475-76 (1980).

<sup>7</sup> See *Grimes*, 782 A.2d at 849-51.

<sup>8</sup> See Robert Charrow & Jason Ross, *Institutional Review Boards—Are They Science's Answer to Hollywood's Hays Board?*, 5 MED. RES. L. & POL'Y REP. 469 (2006).

The article also questions whether a grantee's voluntary commitment to apply federal rules to all of its research, irrespective of the funding source, is enforceable, both as a matter of simple contract law and under the Anti-Deficiency Act. Indeed, any attempt to expand the regulatory regime to privately funded, non-FDA related research is not authorized by the Public Health Service Act, the Food, Drug, and Cosmetic Act, or the organic legislation creating the Department of Health and Human Services. Second, the article highlights some of the ambiguities of the current rules, such as what constitutes "research" and when "research" begins.<sup>9</sup> These two sets of issues highlight the inherent tension between those who believe that regulation of science is appropriate and can only serve to enhance the scientific enterprise and those, such as myself, who believe that science can only thrive in an environment relatively free of regulatory hurdles and that prophylactic regulation is to be avoided unless one can empirically demonstrate that private remedies are inadequate.

## I. BACKGROUND

### A. *An Abbreviated History of the Federal Regulation of Human Subjects Research*

The concentration camp "research" of Nazi Josef Mengele focused world attention on immoral and barbarous human experimentation.<sup>10</sup> By contrast, the ethical metes and bounds of legitimate clinical research received relatively scant attention through the 1950s. Clinical research was in its infancy and the research community was relatively innocent, perhaps even naïve. In the 1960s, however, there was a dramatic increase in clinical research owing to a nearly 400-fold increase in National Institutes of Health ("NIH") funding<sup>11</sup> and the Kefauver-Harris Drug Amendments of 1962,<sup>12</sup>

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<sup>9</sup> Many significant issues relating to IRBs—in addition to the ones discussed in this paper—are being debated in academia and in government. My failure to discuss them merely reflects space limitations and does not imply that I view those issues as unimportant. Thus, whether IRBs should be certified by independent accrediting bodies, whether financial conflict of interest rules should be strengthened, and whether the HIPAA privacy rule will adversely affect researchers are important issues that merit attention. There is one issue, though, that I view as unimportant: whether there should be a single government-wide agency to oversee human research. See ELISA EISEMAN, NATIONAL BIOETHICS ADVISORY COMMISSION: CONTRIBUTING TO PUBLIC POLICY 116 (2003). The President's National Bioethics Advisory Commission recommended a single regulatory agency. *Id.* A super-agency is unnecessary, in my view, especially since the vast bulk of clinical research is already under the regulatory aegis of the Secretary of Health and Human Services.

<sup>10</sup> Mengele's "research" was ostensibly aimed at isolating and eradicating inferior genetic strands from the population as a way of creating a German super-race. See Richard S. Saver, *Medical Research and Intangible Harm*, 74 U. CIN. L. REV. 941, 951–52 (2006), and sources cited therein.

<sup>11</sup> The NIH appropriation went from approximately \$2.4 million in 1945 to over \$873 million in 1966. See NIH Almanac, available at <http://permanent.access.gpo.gov/lps5371/2003/almanac2003-4.pdf>.

<sup>12</sup> Pub. L. No. 87-781, § 102, 76 Stat. 780, 781–82 (1962).

which required pharmaceutical companies to demonstrate the efficacy of their drugs through clinical trials.

Innocence was about to be overtaken by two events—a study and a scandal. In 1966, Henry Beecher, a preeminent researcher and anesthesiologist at the Harvard Medical School, posed a simple question: “Nearly everyone agrees that ethical violations do occur. The practical question is, how often?”<sup>13</sup> To answer this question, Beecher reviewed 100 consecutive clinical studies published in 1964 in “an excellent,” but unnamed, journal. He concluded that twelve of the studies were “unethical” and many others raised serious ethical concerns.<sup>14</sup> Beecher was particularly concerned about the apparent lack of informed consent and the frequency with which patients were, for the purposes of the study, denied the best available treatment or, in some cases, any treatment. Beecher’s 1966 study received significant attention in the lay press and would play a pivotal role in the eventual adoption of federal regulations. However, academic studies—especially when the purported miscreants are anonymous—rarely carry the weight necessary to stimulate congressional action. Eight years later, a real scandal burst onto the scene—the syphilis study at Tuskegee.

On July 26, 1972, the *New York Times* reported on the “Tuskegee Syphilis Study,” which, according to the paper, was “the longest nontherapeutic experiment on human beings in medical history.”<sup>15</sup> From 1932 to 1972, as part of a Public Health Service cooperative study, treatment was denied to 399 poor African-American sharecroppers in Macon County, Alabama, who had been diagnosed with syphilis. This was done to permit government scientists to study the natural course of the disease. The revelations in the press shocked the conscience of the nation, although in many respects the type of ethical transgression at the core of the Tuskegee study, namely the denial of treatment, was evident in Beecher’s exposé.

Responding to the Tuskegee study, Congress enacted the National Research Service Award Act in 1974, requiring any entity applying for funding under the Public Health Service Act to submit with its application “assurances satisfactory to the Secretary that it has established a board (to be known as an ‘Institutional Review Board’) to review biomedical and behavioral research involving human subjects.”<sup>16</sup>

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<sup>13</sup> H.K. Beecher, *Ethics and Clinical Research*, 274 N. ENG. J. MED. 1354, 1355 (1966).

<sup>14</sup> In all, Beecher identified 50 studies (including the 12 noted above) that, in his view, raised serious ethical concerns. “[F]or reasons of space,” he was only able to summarize 22 of those studies. *Id.* at 1355.

<sup>15</sup> Jean Heller, *Syphilis Victims in U.S. Study Went Untreated for 40 Years*, N.Y. TIMES, July 26, 1972, at A1.

<sup>16</sup> National Research Service Award Act of 1974, Pub. L. No. 93-348, § 212, 88 Stat. 342, 352–53 (1974); see S. REP. NO. 93-381 (1973). A year before congressional action, the then Department of Health, Education, and Welfare issued a proposed rule (dubbed “proposed policy”) which sought to codify, for the first time, prior NIH policy for protecting human subjects in NIH funded research. See Protection of Human Subjects, 38 Fed. Reg. 27,882 (Oct. 9, 1973). The HEW rule, which was to be

Congress soon realized, however, that this statute was inadequate because it failed to cover most agencies that funded basic research. Thus, as part of the Community Mental Health Centers Extension Act of 1978,<sup>17</sup> Congress created the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research to review the adequacy and uniformity of government-wide policies for protecting human research subjects. In its First Biennial Report, the Commission recommended that uniform federal regulations be adopted.<sup>18</sup> Thereafter, on June 3, 1986, the White House Office of Science and Technology Policy published its Model Federal Policy for Protection of Human Subjects, usually referred to as the "Common Rule."<sup>19</sup> The Common Rule has since been adopted by the relevant agencies with appropriate changes reflecting the individual needs of each agency involved.<sup>20</sup>

### B. *Contours of Government-Wide Policy: A Summary*

1. *Institutional Review Boards.*—The Common Rule covers all federally funded research that involves human subjects and requires that an awardee assure the agency that it will comply with the agency's policies on human subjects.<sup>21</sup> In general, this means that the awardee will create an Institutional Review Board to review the risks and benefits of any proposed research involving human subjects. Each IRB must have at least five members, with varying backgrounds; at least one member must be a non-scientist and at least one person must not be affiliated with the institution.<sup>22</sup> The IRB must review, discuss, and approve any research involving human subjects before that research can be funded by the government. Research involving "minimal risk" can be approved, on an expedited basis, by a sin-

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codified at 45 C.F.R. part 46, was to govern all research programs funded by HEW. *Id.* A final rule was issued the following year. *See* Protection of Human Subjects, 39 Fed. Reg. 18,914 (May 30, 1974).

<sup>17</sup> Pub. L. No. 95-622, § 1801, 92 Stat. 3412, 3438–39 (1978).

<sup>18</sup> *See* Protection of Human Subjects, 47 Fed. Reg. 13,272, 13,274 (March 29, 1982). Normally, federal regulation of grants and contracts is exempt from the normal notice and comment requirements of the Administrative Procedure Act. *See* 5 U.S.C. § 553(a)(2). However, the Secretary of Health and Human Services voluntarily agreed to abide by the notice and comment requirements even when requirements would not apply. *See* Public Participation in Rule Making, 36 Fed. Reg. 2532 (proposed Feb. 5, 1971); *see also* *Humana of S.C. v. Mathews*, 419 F. Supp. 253, 260 (D.D.C. 1976) (holding in dictum that the Richardson waiver is binding on the Secretary).

<sup>19</sup> *See* Model Federal Policy for Protection of Human Subjects, 51 Fed. Reg. 20,204 (June 3, 1986) (hereinafter *Common Rule*).

<sup>20</sup> The most widely referenced codification of the Common Rule is the one issued by HHS, the largest funder of biomedical research. *See* 45 C.F.R. pt. 46 (2006).

<sup>21</sup> There used to be an extraordinarily convoluted system by which a putative grantee assured NIH that it was complying or would comply with the Common Rule. Entities could file any one of a number of different types of assurances. That system is being replaced by a single Federalwide Assurance that provides grantees with significantly more flexibility than the Byzantine system it replaces. *Research Projects Involving Human Subjects*, 66 Fed. Reg. 19,141 (Apr. 13, 2001).

<sup>22</sup> *See* 45 C.F.R. § 46.107 (2006).

gle designated member of the IRB (usually the chairperson); the research need not be reviewed or approved by the full board.<sup>23</sup> In the course of considering the proposed research, the IRB must identify and weigh its risks against its potential benefits. At least annually, the IRB must review and approve any application for continuing the research.

2. *Informed Consent.*—As part of its evaluation process, the IRB must weigh the potential risks posed by the research against any possible benefits and must also review and approve the informed consent form that usually must be signed by each human subject. Indeed, research involving human subjects usually can be conducted only after these subjects have signed a duly approved informed consent form that meets the regulatory requirements and includes, among other things, the risks and benefits of the proposed study, appropriate alternative procedures, an acknowledgement that the subject can cease participating whenever he or she wishes, and a discussion of the possible significance of the research.<sup>24</sup>

3. *Record Retention.*—Each IRB is required to maintain records, including the grant application, informed consent forms, minutes of meetings, and disposition for each proposed research protocol involving human subjects, for such periods as the funding agency specifies in its regulations. For example, the Department of Health and Human Service (“HHS”) rules require that IRB records be maintained for at least three years after completion of the research at issue.<sup>25</sup>

4. *Sanctions.*—Funding agencies reserve the right to sanction grantees found to have violated the agency’s human-subjects regulations. The method and severity of the sanction varies across agencies. At the National Science Foundation (“NSF”), for example, violations of that agency’s human subjects regulations are investigated by the NSF Inspector General and can constitute “scientific misconduct.”<sup>26</sup> In contrast, at HHS such investigations are conducted by the Office for Human Research Protections (“OHRP”).<sup>27</sup> At HHS, a grant may be terminated or suspended if there is a finding that there has been a “material[] fail[ure] to comply with the terms of [the HHS human subjects] policy.”<sup>28</sup> If the problems are deemed sys-

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<sup>23</sup> See 45 C.F.R. § 46.110 (2006); Research Activities Which May Be Reviewed Through Expedited Review, 46 Fed. Reg. 8392 (Jan. 26, 1981) (listing ten types of research that automatically qualify for expedited review).

<sup>24</sup> See 45 C.F.R. § 46.116 (2006).

<sup>25</sup> See 45 C.F.R. § 46.115(b) (2006).

<sup>26</sup> See 45 C.F.R. pt. 689 (2005).

<sup>27</sup> OHRP replaced the Office for Protection Against Research Risks (“OPRR”), which had been part of the National Institutes of Health. See Statement of Organization Functions, and Delegation of Authority, 65 Fed. Reg. 37,136 (proposed June 13, 2000). OHRP, as was the case for OPRR, is burdened with an overly bureaucratic, noun-string name.

<sup>28</sup> 45 C.F.R. § 46.123(a) (2006).

temic, OHRP may suspend all human subjects research at the institution except for patient follow-up. In extraordinary cases, a federal agency, such as HHS, can seek to debar the institution, the investigator, or both.<sup>29</sup>

In addition to administrative sanctions, failure to adhere to human subjects regulations can subject researchers and their institutions to actions for assault, battery, and negligence, and can jeopardize intellectual property interests that are based on tissue removed from a patient as part of study.<sup>30</sup>

### C. *The Food and Drug Administration: An Uncommon Rule*

Regulation of clinical research by the FDA, while comparable in many respects to regulation by other funding agencies that follow the Common Rule, differs in one key respect. The Common Rule is a child of the Spending Clause—the constitutional provision that authorizes the federal government to spend money and, by implication, to impose conditions on the receipt of that money.<sup>31</sup> In contrast, the FDA derives its jurisdiction from the Commerce Clause.<sup>32</sup> As a result, while the Common Rule only governs federally funded research, the FDA's jurisdiction extends to all clinical research involving new drugs, devices or biologics to the extent that interstate commerce is implicated; purely intrastate activity is, in theory, beyond the reach of FDA.<sup>33</sup>

The FDA's jurisdiction over clinical drug trials (as well as devices and biologics) is extremely broad because the very act of administering an unapproved drug to a human is unlawful unless the FDA permits the experimental use. Specifically, under the Food, Drug, and Cosmetic Act, subject to limited exceptions, a drug that has not been approved for marketing by

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<sup>29</sup> See OHRP, INSTITUTIONAL REVIEW BOARD GUIDEBOOK ch. I, at 10 (1993), available at [http://cnmml.columbia.edu/projects/rcr/rcr\\_conflicts/misc/Ref/OHRP\\_IRB.pdf](http://cnmml.columbia.edu/projects/rcr/rcr_conflicts/misc/Ref/OHRP_IRB.pdf); 45 C.F.R. pt. 76 (2005).

<sup>30</sup> See Robert Charrow, *Wheat, Guns and Science: The Commerce Clause and Human Subjects*, 9 J. NIH RES. 55, 56 (1997); Robert Charrow, *Whose Tissue Is It Anyway?*, 6 J. NIH RES. 79, 79–80 (1994); Robert Charrow, *Informed Consent: From Canterbury Tales to Canterbury v. Spence*, 5 J. NIH RES. 75, 80 (1993).

<sup>31</sup> See U.S. CONST. art. I, § 8, cl. 1; *South Dakota v. Dole*, 483 U.S. 203, 212 (1987) (upholding, as a valid exercise of federal authority under the Spending Clause, a federal law that conditioned the receipt of federal highway funds on the State's adoption of a minimum drinking age of 21). The National Research Service Award Act of 1974, the statutory basis for the regulation of human subjects research at HHS, hinges receipt of federal funds on a grantee's assurance that it will conduct the federally funded research in accordance with the rules adopted by the Secretary. See Pub. L. No. 93-348, §472, 88 Stat. 342 (1974) (codified at 42 U.S.C. § 289(a) (2000)).

<sup>32</sup> U.S. CONST. art. I, § 8, cl. 3.

<sup>33</sup> See *United States v. Lopez*, 514 U.S. 549, 556–57 (1995) (invalidating a federal law banning guns within a school zone as not sufficiently tied to interstate commerce); *United States v. Morrison*, 529 U.S. 598, 618–19 (2000) (invalidating federal law creating private right of action for gender-based violence as lacking a foundation under the Commerce Clause). *But see* *Gonzales v. Raich*, 545 U.S. 1, 22 (2005) (overturning California's Compassionate Use Act, which authorized limited marijuana use for medicinal purposes even though the marijuana at issue was entirely intrastate).

the FDA is called a “new drug.”<sup>34</sup> A new drug is automatically misbranded and probably adulterated.<sup>35</sup> It is unlawful to deliver, receive or introduce into interstate commerce any drug or device that is adulterated or misbranded.<sup>36</sup> It is also unlawful under 21 U.S.C. § 331(d) to introduce or deliver an unapproved new drug. However, the law allows the Secretary of HHS, acting through the Commissioner of Food and Drugs, to grant exemptions “from the operation of the [New Drug provisions of the Food, Drug and Cosmetic Act] [for] drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs.”<sup>37</sup> Given that a clinical trial of a new drug proceeds at the sufferance of the FDA, the agency requires investigators to execute a contract with the agency promising, among other things, to follow all of the applicable rules.<sup>38</sup>

Although FDA jurisdiction is broad, it is not exclusive; researchers may be subject to overlapping jurisdictions. For example, where a researcher receives NIH funding to conduct a clinical trial of a new biologic, the research and researcher fall within the jurisdiction of both OHRP and the FDA. If the article being tested involves recombinant technology, then the research would also fall within the jurisdiction of NIH’s Office of Biotechnology Activities.<sup>39</sup>

Operationally, FDA rules tend to mirror the Common Rule.<sup>40</sup> There are noteworthy differences between the two, though, primarily with regard to reporting and sanctions.

*I. FDA Reporting Requirements.*—Adverse event reporting is critical—it enables an IRB or the FDA to reevaluate whether a protocol is posing greater risks than may have originally been thought. It is not uncommon for an IRB or the FDA to halt a study after receiving a bevy of unexpected adverse event reports. Despite the critical importance of adverse event reporting, the Common Rule’s reporting obligations are vague: a researcher is required to report promptly to his or her IRB “any unanticipated problems involving risks to subjects or others.”<sup>41</sup>

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<sup>34</sup> 21 U.S.C. § 321(p) (2000).

<sup>35</sup> See 21 U.S.C. §§ 351–352 (2000).

<sup>36</sup> See 21 U.S.C. § 331(a)–(c) (2000).

<sup>37</sup> 21 U.S.C. § 355(i) (2000).

<sup>38</sup> See FDA Form 1572, available at <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf>. Those seeking to sponsor an investigation trial must file an Investigational New Drug (“IND”) application (for drugs and biologics) or Investigational Device Exemption (“IDE”) application (for devices). See Investigational New Drug Application, 21 C.F.R. pt. 312, subpt. B (2006); 21 C.F.R. pt. 812 (2006).

<sup>39</sup> See Recombinant DNA Research, 65 Fed. Reg. 77,655 (proposed Dec. 12, 2000).

<sup>40</sup> See 21 C.F.R. pts. 50, 54, 56, 812 (2006).

<sup>41</sup> 45 C.F.R. § 46.103(b)(5)(i) (2006).

In contrast, the FDA reporting requirements are considerably more refined. They differentiate between the investigator (i.e., the researcher supervising those who administer the experimental drug or biologic or use the device) and the sponsor (i.e., the entity that obtains permission from the FDA to use an experimental drug, biologic or device in or on humans). The investigator is required to provide the sponsor with all the information that the sponsor needs to provide to the FDA.<sup>42</sup> In turn, the sponsor must report to the FDA “[a]ny adverse experience associated with the use of the drug that is both serious and unexpected” within 15 days of receipt of the information, or within 7 days if the adverse experience threatens the life of a human subject or results in a subject’s death.<sup>43</sup> The rules further define the terms “serious adverse drug experience,” “unexpected adverse drug experience,” “associated with the use of the drug,” and “life-threatening adverse drug experience.”<sup>44</sup> Sponsors are also required to advise the FDA whenever other research or findings suggest that the risks associated with the experimental drug are more significant than originally thought.<sup>45</sup> Finally, sponsors are required to summarize annually for the FDA various events, including all deaths of test subjects irrespective of their cause.<sup>46</sup> Thus, by way of example, under the FDA rules, a sponsor (and by implication an investigator) must report all subjects who died as a result of an automobile accident or other causes arguably unrelated to the experimental treatment.

2. *Sanctions.*—The FDA has an unusually wide array of available sanctions, some innocuous, others onerous. With respect to investigators, the most common and least onerous sanction is a letter requesting that the investigator respond to a series of deficiencies that the FDA has found during an inspection of the investigator’s records.<sup>47</sup> If the deficiencies are more serious and the investigator’s response to an earlier letter is not adequate, the FDA may send a Warning Letter. Warning Letters are published on the FDA website. If the deficiencies are significant (i.e., the investigator has “repeatedly or deliberately” violated FDA rules), the FDA can seek to disqualify the investigator from receiving investigational new drugs.<sup>48</sup> Investi-

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<sup>42</sup> See 21 C.F.R. § 312.64(a).

<sup>43</sup> See 21 C.F.R. § 312.32(c)(1)(A)–(c)(2).

<sup>44</sup> See 21 C.F.R. § 312.32(a).

<sup>45</sup> See 21 C.F.R. § 312.32(c)(1)(B).

<sup>46</sup> See 21 C.F.R. § 312.33(b)(1)–(4).

<sup>47</sup> FDA is authorized by the Federal Food, Drug, and Cosmetic Act to inspect sites that conduct clinical trials. See 21 U.S.C. §§ 372–374 (2000). Investigators are obligated to permit such inspections. *Id.* FDA inspectors record their observations on Form 483. The form is provided to the researcher at the end of the inspection. Inasmuch as the data collected from a clinical trial of a new drug will be used by the sponsor to support a New Drug Application, the FDA normally inspects patient records at sites that have enrolled relatively large numbers of patients to ensure the accuracy of data and compliance with FDA rules. See Martin Shapiro and Robert Charrow, *Scientific Misconduct in Investigational Drug Trials*, 312 N. ENG. J. MED. 731, 732 (1985).

<sup>48</sup> See 21 C.F.R. § 312.70(a).

gators who have been disqualified by the FDA are listed on an agency web site, as are those whom the FDA is seeking to disqualify.

## II. EMERGING ISSUES

### A. *Expanding Coverage of the Common Rule to Non-Federally Funded Research*

1. *Possible Legal Constraints.*—Recently, there have been two efforts—one legislative and the other quasi-regulatory—to extend the reach of the Common Rule. In 1997, then-Senator John Glenn (D-Ohio), the ranking member of the Senate Governmental Affairs Committee, introduced the Human Research Subject Protections Act of 1997,<sup>49</sup> which sought to extend federal regulation of research involving human subjects to include all research, whether federally funded or not, involving humans. Hearings were never held on Glenn’s proposal; it was reintroduced during the 106th, 107th, 108th, and 109th Congresses by Rep. Diana DeGette (D-Colo.), but each time the bill died in committee.<sup>50</sup>

Legislation such as the proposals introduced by Glenn and DeGette raises significant constitutional issues. First, it is questionable whether the Commerce Clause would accommodate a proposal that seeks to extend federal authority to areas that have been within the traditional jurisdiction of the States. Under *United States v. Lopez*, where the Court invalidated the Gun-Free School Zones Act of 1990, the relevant test appears to be whether the conduct Congress seeks to regulate, in this case human experimentation conducted outside the Common Rule, “substantially affects” interstate commerce. Whether human experimentation is characterized, like education in *Lopez*, as an inherently non-commercial undertaking or as a fundamental feature of a technology-based economy may be more telling, though, than its actual impact on interstate commerce.<sup>51</sup>

While congressional involvement remains a possibility, the more interesting extension of federal regulatory jurisdiction over research involving human subjects appears to be taking place voluntarily. As part of the federal government-wide assurance process, grantees are asked whether they will voluntarily agree “to assure compliance with the Terms of the Assurance for all of its human subject research, regardless of funding source.”<sup>52</sup> Whether such a voluntary agreement absent federal funding is enforceable

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<sup>49</sup> See S. 193, 105th Cong. (1997).

<sup>50</sup> See H.R. 5578, 109th Cong. (2006); H.R. 4605, 106th Cong. (2000).

<sup>51</sup> See *United States v. Morrison*, 529 U.S. 598, 617 (2000) (rejecting the argument that “Congress may regulate noneconomic, violent criminal conduct based solely on that conduct’s aggregate effect on interstate commerce”).

<sup>52</sup> See DEP’T OF HEALTH & HUMAN SERVS., FEDERALWIDE ASSURANCE OF PROTECTION FOR HUMAN SUBJECTS 4 (2002).

is open to serious doubt for two reasons. First, as a matter of basic contract law (and a grant is a contract<sup>53</sup>), provisions that lack consideration are usually unenforceable, unless, of course, there is reliance.<sup>54</sup> It is difficult to envision how the government could come to rely on a promise that has nothing to do with government-funded research.

Second, even if the provision were somehow deemed enforceable as a matter of basic contract law, OHRP likely lacks the authority to do that enforcing. The Secretary's basic authority over non-FDA regulated research does not appear to extend to privately funded studies, although the organic legislation is less than a model of clarity. Specifically, the National Research Service Award Act of 1974, discussed earlier, provides in pertinent part:

(a) The Secretary shall by regulation require that each entity which applies for a grant or contract under [the Public Health Service Act] for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit . . . assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an "Institutional Review Board") to review biomedical and behavior research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research.<sup>55</sup>

As originally enacted, the provision is not plainly limited to research projects funded by government; it arguably authorizes the Secretary to require putative grantees to use IRBs for all research conducted at the institution irrespective of the funding source. However, in 1985, when Congress provided the Secretary with explicit enforcement authority, it limited that authority to federally funded projects. Specifically, the Extension Act provided as follows:

The Secretary shall establish a process for the prompt and appropriate response to information provided to the Director of NIH respecting incidences of violations of the rights of human subjects of research *for which funds have been made available under this chapter*. The process shall include procedures for the receiving of reports of such information from recipients of funds under this chapter and taking appropriate action with respect to such violations.<sup>56</sup>

The Secretary's enforcement authority is thus limited to research that has actually been funded under the Public Health Service Act. Not surprisingly, given this lack of authority over non-federally funded research, no funds

<sup>53</sup> See *Trustees of Dartmouth College v. Woodward*, 17 U.S. (4 Wheat.) 518, 627 (1819).

<sup>54</sup> See RESTATEMENT (SECOND) OF CONTRACTS §§ 71, 90 (1979).

<sup>55</sup> National Research Service Award Act of 1974, Pub. L. No. 93-348, § 212, 88 Stat. 342, 352-53 (amending the Public Health Service Act by adding a new section 474).

<sup>56</sup> Health Research Extension Act of 1985, Pub. L. No. 99-158, § 491, 99 Stat. 820, 861-62 (codified at 42 U.S.C. § 289(b)(2) (2000)) (emphasis added) (amending the Public Health Service Act by adding a new subsection (b) to existing section 474).

have been appropriated to HHS for the purpose of policing privately funded research. Lacking appropriated funds, it is unlawful, under the Anti-Deficiency Act, for an agency official to “make or authorize an expenditure or obligation exceeding an amount available in an appropriation or fund for the expenditure or obligation.”<sup>57</sup> Indeed, the government normally cites to the Anti-Deficiency Act as a reason why it cannot take certain actions championed by various interest groups or satisfy certain judgments.<sup>58</sup> In *United States v. Nave*, the court, in denying a court appointed counsel’s motion for lodging during trial of an indigent defendant, noted that,

under the so-called Anti-Deficiency Act, the Court should not order such an expenditure, see 31 U.S.C. § 1341, and, if it were to do so, the undersigned judge could conceivably be open to criminal prosecution under 31 U.S.C. § 1350, a situation that might mildly amuse some, but which ought to be avoided, if possible.<sup>59</sup>

Thus, even if a university voluntarily agrees to subject all of its research to the Common Rule, that promise cannot be enforced by the Secretary or OHRP without violating the Anti-Deficiency Act.

2. *Policy Concerns.*—There are reasons other than legal ones for questioning the wisdom of extending the Common Rule to privately funded, non-FDA regulated research. The current regulatory scheme is, at best, twice removed from actually assuring subjects’ safety. The Common Rule requires that an IRB weigh the risks versus the benefits of any proposed research. The IRB is required to prove that it discharged this responsibility. That proof usually consists of the minutes of the IRB meeting noting the concerns, if any, voiced by the members and the vote to approve the protocol. OHRP, in conducting its compliance review, appears to focus on the existence and quality of the proof that the process was performed, and not on whether anyone was injured in the study or whether the IRB’s assessment was correct.

Does it make sense to invest additional resources in a compliance scheme that is, in fact, remarkably removed from the research itself, or does it make more sense to rely on the tort system to correct any problems? Does a dual system for protecting human research subjects’ interests—regulatory and tort—make sense? Interestingly, the data necessary to answer these and related questions are conspicuously absent. In short, before we seek to further regulate research, it may make sense to develop the type

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<sup>57</sup> 31 U.S.C. § 1341(a)(1)(A) (2000).

<sup>58</sup> See *Cherokee Nation of Oklahoma v. Leavitt*, 543 U.S. 631, 642 (2005); *Star-Glo Assoc., LP v. United States*, 414 F.3d 1349, 1354 (Fed. Cir. 2005); cf. *E.I. Du Pont De Nemours & Co. v. United States*, 365 F.3d 1367, 1374 (Fed. Cir. 2004) (discussing, without deciding, whether the Anti-Deficiency Act prohibits the government from agreeing to an open-ended indemnification).

<sup>59</sup> 733 F. Supp. 1002, 1002–03 (D. Md. 1990).

of data called for by the Regulatory Flexibility Act<sup>60</sup> and the Unfunded Mandates Act.<sup>61</sup> After all, if we are to further regulate research, we should at least do so in a scientific way, namely gathering data before reaching conclusions.

*B. Research—What Is It and When Does It Begin?*

The Common Rule defines research as “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.”<sup>62</sup> A hypothetical involving interviews with individuals, which can easily fall within this definition, illustrates the potential vagueness, overbreadth, and ambiguity inherent in the Common Rule as applied to social science. Suppose that a journalism professor and a psychology professor from separate state universities collaborate on a study of whether a jury properly convicted an individual tried 10 years earlier. Part of the study is aimed at assessing the reliability of certain types of testimony. A major newspaper has already asked the collaborators to describe their findings in a lengthy article for the paper’s Sunday supplement; their article will call for changes in the rules of evidence. Are the two conducting research? If so, is the state university that employs the journalism professor precluded by the First Amendment and the law of prior restraint from requiring IRB approval? At the least, *Rust v. Sullivan*<sup>63</sup> suggests that, even under the Spending Clause, attempts to regulate this type of research at a university raise significant First Amendment issues, especially where the regulation amounts to a prior restraint. The *Rust* Court, in upholding conditions on family planning grants, nonetheless stressed that,

the university is a traditional sphere of free expression so fundamental to the functioning of our society that the Government’s ability to control speech within that sphere by means of conditions attached to the expenditure of Government funds is restricted by the vagueness and overbreadth doctrines of the First Amendment.<sup>64</sup>

Indeed, vagueness and overbreadth are flaws that are readily found in most attempts to regulate research. Defining what it means to conduct “research” is a formidable task, one that philosophers of science and epistemologists have grappled with for centuries.<sup>65</sup> There is no reason to believe

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<sup>60</sup> See 5 U.S.C. §§ 600–612 (2000).

<sup>61</sup> See 2 U.S.C. §§ 1501–1571 (2000).

<sup>62</sup> 45 C.F.R. § 46.102(d) (2006).

<sup>63</sup> 500 U.S. 173 (1991).

<sup>64</sup> *Id.* at 200 (citing *Keyishian v. Board of Regents*, 385 U.S. 589, 605–06 (1967)).

<sup>65</sup> Compare IMMANUEL KANT, *CRITIQUE OF PURE REASON* (Robert Hutchinson ed., J.M.D. Meiklejohn trans., Encyclopedia Britannica 1989) (1781), KARL R. POPPER, *THE LOGIC OF SCIENTIFIC DISCOVERY* (rev. ed. 1972), and FRANCIS BACON, *THE NEW ORGANON OR TRUE DIRECTIONS CONCERNING THE INTERPRETATION OF NATURE* (1620) (James Spedding et al. trans., 1863), with *Com-*

that the drafters of regulations such as the Common Rule have achieved any more success than have Bacon and Popper.

If the journalism professor is protected by the First Amendment, what about the psychology professor? Should a university use a *Daubert*-type test, e.g., was the scientific method used, to ascertain whether faculty members are conducting research?<sup>66</sup> These are perplexing issues and illustrate the limitations of the Common Rule. These limitations, however, have not been adequately addressed by OHRP and there is nothing to indicate that OHRP has the necessary expertise or sensitivity to evaluate First Amendment considerations: a bureaucrat never lost his or her job by saying “no.”

Usually, it is relatively easy to ascertain whether a project involves research. However, it may be less than clear when the research begins. Ascertaining when research begins is critical since the research may proceed only after informed consent has been given.<sup>67</sup> Suppose, for example, that a researcher is testing a new drug aimed at treating certain types of angina. Only patients who have been admitted to the hospital suffering from severe chest pains are eligible to participate. The entrance criteria for the study also require a specific white blood cell count and a negative HIV test. The blood work is routinely performed by the hospital on all new admissions, but an HIV test is not routinely performed. Does the study begin at the time of hospitalization, at the time of the blood is drawn, at the time the HIV test is ordered, or at some other time?

As a general rule, screening tests to ascertain eligibility of human subjects to participate in a study are considered part of the study and may not be undertaken unless informed consent has been obtained.<sup>68</sup> However, where laboratory tests, for instance, are part and parcel of a patient’s treatment and are routinely performed on all patients—whether they participate in a study or not—then those tests should not trigger the “start” of a study even if results from those tests are used to ascertain eligibility. In contrast, laboratory tests that would not have been performed but for the study are sufficient to trigger the start of a study.

#### CONCLUSION

Regulating non-federally funded, social science research is unwise: it misallocates resources and can raise a host of legal issues. When such en-

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*mon Rule*, *supra* note 19, at 20,206. “It is probably impossible to spell out cogently in a few sentences what we mean by scientific research. The Common Rule is a testament to the notion that not all ideas can be reduced to a few sentences.” Charrow & Ross, *supra* note 8, at 472.

<sup>66</sup> See *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

<sup>67</sup> See 45 C.F.R. § 46.116 (“[N]o investigator may involve a human . . . as a subject . . . unless the investigator has obtained the legally effective informed consent . . .”).

<sup>68</sup> See U.S. FOOD & DRUG ADMIN., INFORMATION SHEETS, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS: 1998 UPDATE, at 9 (1998) (“[I]nformed consent must be obtained prior to initiation of any clinical procedures [including screening tests] that are performed *solely* for the purpose of determining eligibility for research . . .” (emphasis added)).

forcement is undertaken by OHRP, it is likely illegal and, in theory, could expose OHRP employees to criminal prosecution for violating the Anti-Deficiency Act. When such enforcement is undertaken by state officials pursuant to state law, then there is a distinct probability that the state law is overbroad.<sup>69</sup>

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<sup>69</sup> See Charrow & Ross, *supra* note 8, at 472; Philip Hamburger, *The New Censorship: Institutional Review Boards*, 2004 SUP. CT. REV. 271, 290.

