

## REGULATORY PARADOX: A REVIEW OF ENFORCEMENT LETTERS ISSUED BY THE OFFICE FOR HUMAN RESEARCH PROTECTION

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### INTRODUCTION

Writing in 2001, the National Bioethics Advisory Commission (“NBAC”) complained that Institutional Review Boards (“IRBs”) were overwhelmed not only by high workloads and limited resources but also by “a regulatory system that often distracts from rather than focuses on key ethical issues.”<sup>1</sup> NBAC blamed “emphasis by regulators on procedure” for contributing to “an atmosphere in which review of research becomes an exercise in avoiding sanctions and liability rather than in maintaining appropriate ethical standards and protecting human participants.”<sup>2</sup>

The procedure-prone regulator of greatest concern to NBAC was the federal Office for Human Research Protection (“OHRP”). OHRP is the primary government agency responsible for enforcing the federal human subject protection regulations, known as the Common Rule,<sup>3</sup> at the nearly 10,000 federally funded institutions in the country.<sup>4</sup> NBAC judged that OHRP’s focus on paper evidence of procedural compliance was frustrating IRBs and researchers trying to focus on ethical principles.<sup>5</sup> IRBs might properly “review research in accordance with an appropriate focus on ethi-

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\*\* Associate, Conrad O’Brien Gellman & Rohn, Philadelphia, Pa. J.D., Temple Law School, 2006.

<sup>1</sup> NAT’L BIOETHICS ADVISORY COMM’N, 1 ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS 8 (2001).

<sup>2</sup> NAT’L BIOETHICS ADVISORY COMM’N, *supra* note 1, at 13.

<sup>3</sup> Statement of Organization, Functions, and Delegations of Authority, 65 Fed. Reg. 37,136–37 (June 13, 2000) [hereinafter Statement of Organization].

<sup>4</sup> Office for Human Research Protection Fact Sheet, <http://www.hhs.gov/ohrp/about/ohrfactsheet.pdf> (last visited Nov. 12, 2006).

<sup>5</sup> NAT’L BIOETHICS ADVISORY COMM’N, *supra* note 1, at 13.

cal behavior,” but nonetheless run into trouble at OHRP, where “they are ultimately held responsible primarily for procedure and documentation.”<sup>6</sup>

NBAC identified the fundamental challenge for a system of protecting human subjects that embeds reflection on ethical principles in a set of mandated regulatory procedures. The logic of philosophical ethics is open-textured deliberation about how general principles illuminate unique cases, conducted with an appreciation of ambiguity and the value of differing viewpoints. The logic of hierarchical regulation is rigorous compliance with general rules, carefully and uniformly documented, with serious sanctions for non-compliance. The two logics could conceivably coexist with some degree of coherence in some situations. In the case of the human subject protection system, however, observers have persistently noted a tendency towards formal bureaucratic enforcement and compliance largely unrelated and possibly detrimental to ethical behavior.<sup>7</sup> IRBs are required, on behalf of universities and other research institutions, to ensure that research on human subjects comports with indeterminate standards of beneficence, justice, and autonomy, a task which in turn requires IRBs to make fine judgments about small or unknown risks and benefits. Because the quality of an IRB’s deliberations, let alone the “accuracy” of its ethical decisions, cannot readily be verified, institutional compliance with federal regulations is measured almost entirely by review of records and consent forms. The metric, in turn, drives the compliance priorities of the regulated institutions.

In this Article, we examine OHRP’s enforcement activities since the NBAC report. Part I describes OHRP’s work and the methods we used to study it. In Part II, we present our results, which show that OHRP continues to promote ethics by requiring paperwork in just the way NBAC decried. The discussion (Part III) explains why it is too easy to blame the agency, which in many ways seems to be performing in model regulatory fashion. The heart of the problem is the paradoxical scheme of embedding virtue in federal regulations, and then constructing an enforcement system that purports to encourage reflection and deliberation but must in practice enforce procedural diligence and paperwork.

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<sup>6</sup> *Id.* The National Bioethics Advisory Commission (NBAC) added:

OHRP’s *Compliance Activities: Common Findings and Guidance* . . . reflects this emphasis on the regulations by focusing on the procedures by which protocols are reviewed—for example, inappropriate use of expedited reviews and exemptions, lack of a quorum, less than continuing review, and failure to document required findings or votes . . . .

*Id.*

<sup>7</sup> See U.S. GEN. ACCOUNTING OFFICE, *SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS* (1996); OFFICE OF INSPECTOR GEN., DEP’T OF HEALTH AND HUMAN SERVS., *INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM* (1998); NAT’L BIOETHICS ADVISORY COMM’N, *supra* note 1; PANEL ON INSTITUTIONAL REVIEW BDS., SURVEYS, AND SOC. SCI. RESEARCH & NAT’L RESEARCH COUNCIL, *PROTECTING PARTICIPANTS AND FACILITATING SOCIAL AND BEHAVIORAL SCIENCES RESEARCH* (Constance F. Citro et al. eds., 2003) [hereinafter PANEL ON IRBS].

The OHRP's regulatory impact is just one of many issues roiling the enterprise of human research subject protection. In 1966, the *New England Journal of Medicine* published Henry Beecher's damning catalogue of human research subject abuses in medical research, which galvanized the movement to regulate research with human subjects.<sup>8</sup> In 2004, it published Tu and his colleagues' account of a failed effort to create a national stroke registry in Canada, a failure they attributed to the requirement that each person included in the registry give informed consent.<sup>9</sup> The two studies define the arc of a pendulum of human subject protection and the role of ethics in research. No one would wish a return of the sorts of attitudes and practices reported by Beecher, but we have reached the point at which we are over-regulating low risk research and, in too many cases, undermining the conduct of humane, socially beneficial and scientifically excellent studies. This is not to say that the Common Rule is a complete failure; on the contrary, IRBs regularly improve the ethicality of studies and help promote ethical consciousness in researchers. Our study does suggest that fundamental changes in the system will be required to solve the problems identified by NBAC and other critics.

## I. BACKGROUND AND METHODS

### A. OHRP's Work

The OHRP was created in 2000 in response to alleged failures by IRBs and calls for a stronger regulatory oversight role for the federal government.<sup>10</sup> Reflecting a trend toward "strong protectionism" in human subject research,<sup>11</sup> the oversight budget and staff have grown significantly. In 1996, the Office of Protection from Research Risks (the predecessor to OHRP) had 14 full-time staff members and a budget of just over \$2.1 million. Ten years later, OHRP had a staff of 40 and a budget of \$7 million per year.<sup>12</sup>

OHRP uses three distinct regulatory strategies in its oversight work. The first is to influence the "design" of human subject protection at regulated institutions. OHRP and research institutions make agreements called "multiple-project assurances," under which institutions promise to comply with the Common Rule and set out the specific procedures they will use to do so.<sup>13</sup> In overseeing these agreements, OHRP has an opportunity to shape

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<sup>8</sup> See Henry K. Beecher, *Ethics and Clinical Research*, 274 *NEW ENG. J. MED.* 1354 (1966).

<sup>9</sup> Jack V. Tu et al., *Impracticability of Informed Consent in the Registry of the Canadian Stroke Network*, 350 *NEW ENG. J. MED.* 1414, 1414 (2004).

<sup>10</sup> See Statement of Organization, *supra* note 3.

<sup>11</sup> J.D. Moreno, *Goodbye to All That: The End of Moderate Protectionism in Human Subjects Research*, 31 *HASTINGS CENTER REP.* 9, 10 (2001).

<sup>12</sup> Telephone Interview with Bernard Schwetz, Dir., OHRP (May 6, 2005) [hereinafter Interview with Bernard Schwetz].

<sup>13</sup> 45 C.F.R. § 46.103 (2005).

key elements of the human subject protection regime at the institution, including the principles to be applied, the number and composition of IRBs, the extent to which non-federally funded research will be regulated, the extent to which the institution will apply its procedures to research that is not actually covered by the Common Rule, and the procedures for IRB operation.

OHRP's second strategy is the compliance investigation, which takes two forms. OHRP carries out a small number of general evaluation site visits aimed at assessing overall institutional compliance (hereinafter compliance audits), either without cause or in response to a serious incident such as the death of a healthy subject. Far more common than compliance audits are what we will call complaint investigations, which arise in response to specific complaints of investigator misconduct or IRB default. These focus on the particular incident raised in the complaint. The majority of complaints come from institutions themselves, which are required to report deficiencies they discover to the OHRP,<sup>14</sup> but complaints also come from research subjects and whistle-blowers. Generally, complaint investigations begin with a request for information and documentation of compliance from OHRP to the institution. The OHRP makes its determination based on review of the institution's response. The Director of OHRP estimated that approximately 90–95% of complaints are resolved through these kinds of contacts without OHRP opening a formal investigation.<sup>15</sup> If it opens a formal case file, OHRP will send a letter to the institution setting out the details of the complaint and asking the institution to prepare a response. In cases involving an investigator's behavior towards a subject, the OHRP relies in most cases on paper reports of investigations conducted by the institutions themselves. OHRP does not specify any standards or procedures for these internal investigations. They vary in intensity, but in some instances involve collection of evidence including testimony of participants and witnesses, as well as review of documents.<sup>16</sup> OHRP usually defers to these institutional findings, but will conduct a site visit where it suspects that the institution itself is unwilling or unable to get to the truth.<sup>17</sup> Site visits ensue in about 10% of formal investigations.<sup>18</sup> The normal remedy for a problem is one or more changes in the problematic study or in the institution's procedures. In severe cases, individual researchers or institutions may be barred from conducting federally funded research.<sup>19</sup>

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<sup>14</sup> U.S. GEN. ACCOUNTING OFFICE, *supra* note 7, at 15.

<sup>15</sup> Interview with Bernard Schwetz, *supra* note 12.

<sup>16</sup> See, e.g., Letter from Robert J. Meyer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office of Human Research Prots., U.S. Dep't of Health and Human Servs., to Richard C. Powell, Vice President for Research and Graduate Studies, Univ. of Ariz. 3 (June 2, 2003).

<sup>17</sup> Interview with Bernard Schwetz, *supra* note 12.

<sup>18</sup> *Id.*

<sup>19</sup> Early Termination of Research Support: Evaluation of Applications and Proposals, 45 C.F.R. § 46.123 (2005).

OHRP's third strategy is to provide information about ethics generally and the federal regulations in particular. The agency accomplishes this goal through educational programs and materials, and through the production of guidelines and interpretation of specific regulatory provisions.<sup>20</sup>

### B. Study Methods

OHRP memorializes its findings from site inspections and complaint investigations in determination letters. We collected every letter dated between January 1, 2002, and June 30, 2004, posted on the agency's website. OHRP's letters do not distinguish between compliance audits and complaint investigations. We classified matters as compliance audits if it appeared from the letters that the investigation entailed system-wide review of institutional compliance. Matters involving only the conduct or review of specific protocols were classified as complaint investigations. Complaint investigations arising from studies being conducted jointly by multiple institutions ("multi-center studies") resulted in identical letters to all institutions involved. These were treated as one incident, and we removed the duplicate letters from the sample. In some cases, the audit or complaint investigation began before our study period. These earlier letters were added to the data set. One of us (J.W.) developed an initial set of problem and remedy categories based on review of the letters and the regulatory requirements of the Common Rule. A second rater (S.B.) then reviewed the letters and the initial categories for consistency, clarity, and fit with the regulations. The categories were revised and the letters recoded.

## II. RESULTS

We identified and downloaded from the OHRP website 271 letters dated between January 1, 2002, and June 30, 2004, and 5 letters issued before the study period. After removing redundant letters arising from multi-center trials, the final data set consisted of 29 letters from compliance audits at 19 institutions, and 126 letters from 91 complaint investigations. Seventy-one of the complaint investigations dealt with clinical studies, primarily studies of new medical treatments, or basic biomedical research.<sup>21</sup> The categories of problems and remedies are set out in Tables 1 and 2. All analyses below are based on the number of distinct complaint investigations

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<sup>20</sup> The OHRP itself divides this category into two: the provision of regulatory guidance on particular aspects of the Common Rule, or on specific questions from institutions; and general education. Interview with Bernard Schwetz, *supra* note 12.

<sup>21</sup> A 1995 study of the work of almost 500 IRBs found that their workloads were comprised of 51% clinical research, 14% behavioral, 9% biomedical and 26% spread across education, social sciences and others. JAMES BELL, JOHN WHITON & SHARON CONNELLY, EVALUATION OF NIH IMPLEMENTATION OF SECTION 491 OF THE PUBLIC HEALTH SERVICE ACT, MANDATING A PROGRAM OF PROTECTION FOR RESEARCH SUBJECTS 16 (1998).

or institutional compliance audits, not the number of letters, studies, or institutions involved.

*Table 1: Types of Problems Specified in OHRP Letters*

<b>Problem</b>	<b>Examples</b>
Faulty informed consent forms	<ul style="list-style-type: none"> <li>– The language was not understandable by the subject.</li> <li>– The form did not contain elements required by the Common Rule.</li> <li>– The form contained exculpatory language or otherwise asked subjects to relinquish rights.</li> </ul>
Faulty informed consent process	<ul style="list-style-type: none"> <li>– The researcher obtained proxy consent when it would have been appropriate to ask the subject.</li> <li>– The subjects’ informed consent was not obtained before the research began (i.e., the researcher asked for consent after the research began, or did not ask at all).</li> <li>– Undue influence or coercion was used to obtain consent.</li> </ul>
Improper waiver of informed consent	<ul style="list-style-type: none"> <li>– An IRB waived informed consent without documenting consideration of the criteria prescribed in the Common Rule.</li> <li>– The IRB was incorrect in determining that the research entailed minimum risk.</li> </ul>
Lack of IRB approval	<ul style="list-style-type: none"> <li>– Research was not subjected to IRB review as required by the Common Rule.</li> </ul>
Unapproved changes	<ul style="list-style-type: none"> <li>– Changes were made in the study protocol following IRB review without notice to and approval by the IRB.</li> </ul>
Risky study	<ul style="list-style-type: none"> <li>– An approved study did not minimize risks to human subjects.</li> </ul>
Deficient reporting of adverse events	<ul style="list-style-type: none"> <li>– An investigator or researcher did not report a problem to the IRB and/or the OHRP or FDA as required.</li> <li>– IRB did not report an adverse event to the appropriate agency (usually the OHRP).</li> <li>– IRB did not appropriately monitor adverse events.</li> </ul>
Deficiencies in IRB procedure and record-keeping	<ul style="list-style-type: none"> <li>– IRB lacked or had a deficiency in a required procedure (e.g., a procedure for ensuring that children, prisoners, and other vulnerable populations are protected).</li> <li>– IRB did not keep appropriate minutes at meetings.</li> <li>– IRB failed to do an annual review of research projects.</li> </ul>
Problems in subject recruitment	<ul style="list-style-type: none"> <li>– Subjects were recruited who did not meet the approved selection criteria.</li> <li>– Unauthorized recruitment methods.</li> <li>– Inequitable recruitment.</li> </ul>
Privacy violations	<ul style="list-style-type: none"> <li>– IRB failed to specify or require measures to protect privacy.</li> <li>– Researchers failed to adequately protect privacy.</li> </ul>

Table 2: Types of OHRP Remedies

<b>Solutions</b>	<b>Explanation</b>
Training	The institution required researchers or IRB members to undergo training.
New Procedure	The institution added a procedure to the IRB's procedures in order to keep the problem from happening again.
New informed consent documents	The institution drafted a new template for informed consent documents or changed the language in an individual document.
New IRB members	The institution either added an additional IRB or changed the makeup of the IRB to ensure more diversity or better compliance with the Common Rule.
Study changed/stopped	One or more studies suspended pending investigation or changes; or the one or more studies were closed permanently.
Tighter privacy procedures	Usually initiated as a response to a privacy violation, included locking up cabinets or placing records in a more secure room.
Staff change	Adjustment of staffing required for IRB or study team.
Researcher excluded	A researcher was suspended or permanently barred from conducting some or all research.

### A. Compliance Audits

Seventeen audits were not-for-cause; two were conducted as a result of identified problems (a healthy subject death and a warning letter to the institution from the FDA, respectively). In the typical compliance audit, OHRP reviews 20–35 randomly-selected study protocols<sup>22</sup> and 1–4 years of meeting minutes.<sup>23</sup> OHRP letters typically praised institutional zeal for human subject protection. For example:

In the course of the OHRP review, the IRB chair, IRB members, and IRB administrative staff displayed an enthusiastic and sincere concern for the protection of human subjects and stated that they view themselves as providing a valuable service to subjects and the research community. Investigators demonstrated a culture of respect for the protection of human subjects and for the IRB process. IRB procedures for continuing review of research appear to be substantive and meaningful. Every individual interviewed expressed the sen-

<sup>22</sup> "Protocol" is the term commonly used for the documents submitted to the IRB describing the studies' goals and methods.

<sup>23</sup> Interview with Bernard Schwetz, *supra* note 12.

timent that the institution has a very strong commitment to the protection of human subjects. The IRB administrative staff were helpful and accommodating to OHRP during the site visit.<sup>24</sup>

The results of not-for-cause audits suggest that OHRP is not detecting widespread, serious breaches of the Common Rule, much less serious risks or harms to human subjects. However, the compliance audit group included a for-cause audit at Johns Hopkins following the death of a healthy volunteer, as well as a number of less dramatic instances that illustrate that even properly approved research can pose serious risks.

*Table 3: Problems in OHRP Compliance Audit Determination Letters (N= 19)*

<b>Problem</b>	<b>Number of Audits Where this Problem Was Found</b>	<b>Percentage</b>
Deficiencies in IRB procedure and record-keeping	17	90%
Faulty informed consent forms	8	42%
Deficient reporting of adverse events	7	37%
Lack of IRB approval	5	26%
Unapproved changes	3	16%
Improper waiver of informed consent	3	16%
Privacy violations	2	11%
Informed consent process	2	11%
Problems in subject recruitment	2	11%
Other problems	2	11%
Risky study	1	5%

*1. Problems Identified.*—Table 3 shows the problems identified in the compliance audits. Problem types cited per audit ranged from 1 to 7, with an average of 2.5, a median of 2 and a mode of 1. Among those institutions with multiple problems cited, there was considerable overlap among the violations found. The same action—changing a consent form or process after approval—might be cited as an improper consent matter and an unapproved change. The rate of deficiencies could not be calculated, because not all letters stated the number of protocols reviewed.

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<sup>24</sup> Letter from Kristina C Borrer, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Sharon A. Brown, Assoc. Vice President for Research, Univ. of Tex.—Austin 2 (June 4, 2003).

The most common problem in compliance audits was a failure to properly follow and document compliance with required procedures. Deficiencies in IRB procedures and record keeping included poorly kept minutes, inappropriate use of expedited review, failure to make or document the required special findings for research involving children, lack of required diversity on the IRB, and poor management of continuing review. There was no indication in the vast majority of these letters that subjects had been harmed or exposed to excessive risk, or indeed in most cases even that an actual violation of the regulations (as opposed to a failure to document compliance) had occurred.

The most serious problem was the death of a healthy volunteer at Johns Hopkins, which triggered national publicity and an urgent OHRP site visit. This was also the only instance in which an OHRP compliance audit detected a study that was unacceptably risky. The OHRP letter is a catalogue of mistakes (or deliberate rule-breaking) by the investigator and failures on the part of the IRB. The protocol and consent form did not list all known risks, or key information about the drug. The study was not approved by a formally convened IRB. The investigator did not report important changes to the protocol and serious unexpected adverse events to the IRB.<sup>25</sup>

The second most frequent problem was faulty consent forms. In 2 of the 8 cases, risks of death or serious injury were omitted or not fully described, though there was no indication that the likelihood of harm was more than remote or that actual injury had transpired. In another case, the missing information consisted of details of procedures the subject would undergo.<sup>26</sup> In others, the problem was more of puffery on benefits ("I may

<sup>25</sup> The letter states:

- (a) . . . the investigators and the JHBMC IRB failed to obtain published literature about the known association between hexamethonium and lung toxicity. Such data was readily available via routine MEDLINE and Internet database searches, as well as recent textbooks on pathology of the lung.
- (b) Use of hexamethonium is not currently approved by the FDA for use in humans, and has never been approved by the FDA for administration via inhalation.
- (c) . . . [T]he JHBMC IRB failed to obtain sufficient information regarding the source, purity, quality, and method of preparation and delivery of the hexamethonium used in the research.
- (d) The hexamethonium bromide used in the research was obtained by the investigators from Fluka US and was labeled "[f]or laboratory use only, not for drug, household, or other uses." The JHBMC IRB was not aware of this information before the investigators administered the hexamethonium to three subjects and the hospitalization of the third subject.
- (e) . . . [T]he JHBMC IRB did not receive or request from the investigators (i) any information regarding the pharmacology and toxicity of inhaled hexamethonium in animals; or (ii) sufficient information regarding the safety of inhaled hexamethonium in humans.

Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office of Human Research Prots., U.S. Dep't of Health and Human Servs., & Michael Carome, Dir., Div. of Compliance Oversight, Office of Human Research Prots., U.S. Dep't of Health and Human Servs., to Edward D. Miller, Dean and Chief Executive Officer, Johns Hopkins Med., Johns Hopkins Univ. Sch. of Med. et al. 3-4 (July 19, 2001) [hereinafter OHRP Letter to Johns Hopkins Univ. (7/19/2001)].

<sup>26</sup> This letter states:

[T]he protocol outlined that, while hospitalized, each subject would be prescribed physical activity

benefit from the procedure by having my stem cells available for future gene therapy research”<sup>27</sup> or omission of boilerplate on points like the consequences of dropping out of the study.<sup>28</sup> In one case, OHRP was concerned that the IRB and investigator were not providing forms in the native languages likely to be spoken by prospective subjects.

Deficient adverse event reporting was found in almost 37% of audits, but in all but one of the letters the problem seems to have been procedural default without indication of any resulting harm to subjects.<sup>29</sup> For example, in one case, the university had identified and halted three problematic studies, but had not timely reported this to OHRP.<sup>30</sup> The one exceptional letter, again from the Hopkins incident, involved an adverse event that, had it been properly addressed, might have prevented the healthy subject’s death later in the study.<sup>31</sup>

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that mimics the individual’s usual physical activity. This was to be determined prior to admission by requiring the subject to complete a physical activity diary and wear an ergometer and accelerometer on at least 2 separate occasions. The protocol also discussed genetic testing of blood samples obtained. The protocol also stated “[I]n the case of subjects enrolling from locations outside the NY metropolitan area, close scrutiny of medical records and discussions with their physicians will be used in place of examination in our outpatient department.” These procedures are not described in the IRB-approved informed consent document.

Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Human Subject Protection, Office of Human Research Prots., U.S. Dep’t of Health and Human Servs., to Thomas Q. Morris, Vice President, Health Sci. Div., Columbia Univ., Health Sci. 4 (June 27, 2002).

<sup>27</sup> Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Human Subject Protection, Office of Human Research Prots., U.S. Dep’t of Health and Human Servs., to Peter O. Kohler, President Or. Health & Sci. Univ. 2 (Dec. 10, 2002).

<sup>28</sup> The Department of Health and Human Services requires that informed consent documents include statements that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. 45 C.F.R. § 46.116(a)(8) (2003).

<sup>29</sup> Federal regulations require institutions to institute procedures to ensure the proper reporting to OHRP of unanticipated problems involving risks to subjects, major instances of noncompliance, or suspension or termination of IRB approval. 45 C.F.R. § 46.103(a) & (b)(5) (2003).

<sup>30</sup> Letter from Robert J. Meyer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office of Human Research Prots., U.S. Dep’t of Health and Human Servs., to Carol Z. Garrison, President, Univ. of Ala.—Birmingham 2 (Mar. 10, 2004).

<sup>31</sup> The Johns Hopkins study entailed exposing healthy volunteers to a chemical called hexamethonium. The substance was not approved as a drug for human use and had known side dangers that were not identified by the investigator or the IRB. The OHRP implied, not unreasonably, that had the investigator reported and the IRB attended to unexpected side effects experienced in the first subject, the real dangers might have come to light before further subjects were exposed:

OHRP finds that the investigators failed to promptly report an unanticipated problem involving risks to subjects to appropriate institutional officials, the IRB, OHRP, and the head of the sponsoring agency as required by HHS . . . . In specific, the investigators failed to promptly report the cough, shortness of breath, and a decrease in pulmonary function experienced for 8 days by the first subject exposed to hexamethonium. OHRP is particularly concerned that the investigators continued to expose additional subjects to inhaled hexamethonium before the symptoms in the first subject were resolved and before reporting the event to the JHBMC IRB.

OHRP Letter to Johns Hopkins Univ. (7/19/2001), *supra* note 25, at 401.

Three letters addressed allegations of faults in the informed consent process. In one case, the complaint was determined to be unfounded. In another, participants underwent screening and other research-related processes before consent was obtained. In the third, the investigator recruited participants over the phone with oral consent rather than using the written consent form as approved by the IRB. In three other letters, OHRP found that IRBs had improperly waived some or all of the requirements for informed consent.<sup>32</sup> In 2 of these 3 cases, the failure was purely one of documentation: the files did not clearly indicate that the regulatory criteria for waiver were satisfied.<sup>33</sup> Only one of the cases involved a finding that the substantive criteria for waiver had been improperly applied.<sup>34</sup>

Two problem types—lack of IRB approval and unapproved changes to an approved study—are useful indicators of researcher attitudes towards the regulatory system.<sup>35</sup> At five sites, OHRP found studies that had not been approved by the IRB, indicating either deliberate non-compliance by the researcher or, more likely, confusion about the applicability of the rules. One charge was deemed unfounded, and one involved only a failure to review a grant application, a practice no longer required. At two sites, studies had been approved by the IRB after research began. In the fifth, the Hopkins audit, OHRP found that protocols were being reviewed by IRBs, but that these IRBs did not meet quorum or other membership requirements. This meant that they were not “IRBs” in strict legal terms and could not legally authorize research.

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<sup>32</sup> If specific criteria are met, an IRB may waive informed consent, 45 C.F.R. § 116 (2003), or the documentation of informed consent, 45 C.F.R. § 117 (2003). Waiver of the usual requirements requires the IRB to document that:

- (1) The research involves no more than minimal risk to the subjects;
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the waiver or alteration; and
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

45 C.F.R. § 116(d) (2003).

<sup>33</sup> See OHRP Letter to Johns Hopkins Univ. (7/19/2001), *supra* note 25, at 5.

<sup>34</sup> See Letter from Carol J. Weil, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office of Human Research Prots., U.S. Dep’t of Health and Human Servs., to Michael M. Gottesman, Deputy Director for Intramural Research, Nat’l Insts. of Health 3 (Mar. 12, 2002) (“IRB failed to recognize in one instance that a waiver under either 45 CFR 46.116(d) or 46.117(c)(2) is not permissible unless the research involves no more than minimal risk to the subjects.”).

<sup>35</sup> See generally Scott Burris & Kathryn Moss, *Researchers’ Views of the Human Subject Protection System: A Qualitative Study*, 1 J. EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS 39 (2006) (reporting on how researchers experience the human subject protection process).

IRBs must review and approve any change in an approved protocol.<sup>36</sup> At three sites, OHRP found studies that had been changed without appropriate IRB oversight. One investigator adopted an unapproved method of recruitment, letters to potential subjects. Another changed the study design (among other things, eliminating a placebo arm), although not in ways that increased the risk to subjects. In the third matter, the IRB approved changes via an expedited review that should have been reviewed at a full IRB meeting.<sup>37</sup>

The Common Rule requires the IRB to ensure that “[w]hen appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.”<sup>38</sup> Over time, IRBs and researchers have apparently adopted a convention of storing (or at least pledging to store) all data, regardless of its sensitivity or lack thereof, in a locked cabinet or computer in a locked room. In one audit, OHRP found that “research records were stored in an unlocked file cabinet in a common area copy room during the day for a two-week period, where individuals not associated with the research may have had easy access to these files, which contained private, identifiable information, and might even have been able to photocopy them.”<sup>39</sup> There was no suggestion that any records had been copied, or that the private information was of a sensitive nature. In the second case, OHRP determined that a study that had qualified for an expedited review on the ground that no identifiers were to be collected was in fact collecting identifiers and then removing them in a second step. Again, there was no suggestion that this process had significantly increased the risk of harm to subjects.

Two instances of faulty subject recruitment were detected. In one case, “subjects were enrolled outside the protocol age range prior to IRB review and approval of the amended protocol.”<sup>40</sup> In the other, OHRP found that the

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<sup>36</sup> 45 C.F.R. § 46.103(b)(4)(iii) (2005). The regulation refers to “proposed changes in a research activity” with no qualifiers of importance or substantiality. See Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Human Subject Protection, U.S. Dep’t of Health and Human Servs., to Mary Beth Burnside, Vice Chancellor for Research, Univ. of Cal.–Berkeley 1–2 (Dec. 3, 2002) [hereinafter OHRP Letter to Univ. Cal.–Berkeley (12/3/2002)] (“HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve *all* proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes . . . .”) (emphasis added).

<sup>37</sup> See OHRP Letter to Johns Hopkins Univ. (7/19/2001), *supra* note 25, at 7. Expedited review entails the use of a subcommittee of the IRB to review and approve some kinds of minimally risky protocols and minor changes to protocols without an IRB meeting. 45 C.F.R. § 46.110 (2003).

<sup>38</sup> 45 C.F.R. § 46.111(a)(7) (2003).

<sup>39</sup> Letter from Kristina C Borrer, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to George F. Kalf, Professor of Biochemistry/Molecular Pharmacology, Assoc. Dean for Scientific Affairs, Dir., Div. of Human Subjects Protection, Office of Scientific Affairs, Thomas Jefferson Univ. 1 (Apr. 15, 2004).

<sup>40</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Antonio M. Gotto,

IRB was not doing enough to ensure that “vulnerable populations”<sup>41</sup> were properly protected during studies. It added:

Options for additional safeguards that could be considered include, but are not limited to the following: (a) independent consent monitors; (b) use of instruments to assess subject comprehension prior to proceeding with research interventions and interactions; (c) implementation of research subject advocates or an ombudsman; and (d) implementation of independent assessment of capacity to consent for potential subjects who may have impaired capacity to consent.<sup>42</sup>

2. *Remedial Measures.*—The most common remedies for problems uncovered by audit were to adopt new internal oversight procedures (typically *additional* procedures); improve training for investigators, staff, or IRB members; recruit new IRB members; and change study or IRB staff.<sup>43</sup>

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Jr., Provost for Med. Affairs and Dean of the Med. College, Joan and Sanford I. Weill College of Med., of Cornell Univ., & Jeffrey M. Cohen, Assoc. Dean, Joan and Sanford I. Weill College of Med., of Cornell Univ. 4 (May 24, 2004).

<sup>41</sup> The Common Rule requires additional safeguards when some or all of the subjects are likely to be vulnerable to coercion or undue influence. “Vulnerable populations” include children, prisoners, mentally disabled persons, and economically or educationally disadvantaged people. 45 C.F.R. § 46.111(b) (2003).

<sup>42</sup> Letter from Michael A. Carome, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to John M. Allen, Assistant Vice President for Scientific Affairs, Office of Scientific Affairs and Biotechnology, Health Sci. Ctr. at Brooklyn, State Univ. of N.Y.—Downstate Med. Ctr., & John O’Hara, Research Found. Campus Operations Manager, Health Sci. Ctr. at Brooklyn, State Univ. of N.Y.—Downstate Med. Ctr. (Apr. 17, 2002). Such procedures, none of which are specified in the Common Rule, could obviously add considerably to the cost and logistical complexity of research. OHRP cites no evidence that these procedures significantly improve the quality of comprehension or are necessary to prevent undue influence. There is considerable evidence that promoting true informed consent is difficult for reasons ranging from subject’s faith in the doctor–researcher to the complicated wording and concepts in the forms. See, e.g., S. Joffe et al., *Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey*, 358 LANCET 1772, 1776 (2001); L.J. White et al., *Informed Consent for Medical Research: Common Discrepancies and Readability*, 3 ACAD. EMERGENCY MED. 745, 748 (1996) (concluding that only 45% of U.S. adults would be able to read an informed consent form at 70% comprehension).

<sup>43</sup> See, e.g., Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Michael Klag, Vice Dean for Clinical Investigation, Johns Hopkins Univ., Sch. of Med. 1–2 (Aug. 23, 2002) (“(1) JHUSOM has implemented a multifaceted education program to ensure that all IRB members, all IRB staff, and all research investigators are educated on an ongoing basis about the ethical principles and regulatory requirements for the protection of human subjects. (2) Since July 2001, JHUSOM has expanded the number of IRBs from two to four and maintains an additional IRB at the Johns Hopkins Bayview Medical Center, resulting in a significant reduction in the volume of research protocols reviewed and overseen by each IRB. The IRB Chairs and members are highly committed to the protection of human subjects and demonstrated an enhanced knowledge of the ethical issues and regulations related to the protection of human subjects. (3) JHUSOM has expanded the resources of its IRB offices. OHRP notes that additional staff have been hired to assist the IRBs and the overall administration of the system for the protection of human subjects. These additional staff include a new Vice Dean for Clinical Investigation, as well as a new regulatory affairs group and an IRB systems support group. (4) JHUSOM has developed and implemented new procedures for the operations of its IRBs, including procedures for (i)

The “other remedy” category included dissolving a virtually inactive IRB<sup>44</sup> and requiring Hopkins to submit to OHRP extensive monthly summaries of IRB procedures, minutes, policies, and research records for more than a year.<sup>45</sup>

*Table 4: Responses to OHRP Compliance Audit Determination Letters (N=19)*

<b>Response</b>	<b>Number of Audits with this Response</b>	<b>Percentage</b>
New procedure	13	68%
Training	6	32%
Study changed/stopped	4	21%
New informed consent documents	4	21%
New IRB members	4	21%
Staff change	2	11%
Other	2	11%
Tightened security	1	6%

In four cases, OHRP or the institution stopped some or all research at the institution until problems were resolved. One concerned an institution that seemed to be doing a limited amount of research and whose system of review had totally broken down. As part of the resolution of OHRP’s concerns, the institution agreed to stop all studies, dissolve its IRB and enter into an amended assurance using an independent IRB.<sup>46</sup> In two other cases, institutions that had been found to have insufficiently rigorous procedures for periodic review of ongoing studies voluntarily suspended some studies pending proper re-review.<sup>47</sup> OHRP’s ultimate tool for forcing compliance is

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format of IRB meetings; (ii) conduct of IRB review of protocols; and (iii) documentation of IRB activities.”).

<sup>44</sup> Letter from Carol J. Weil, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Raymond Menard, Vice President, Administration, Ctr. for Molecular Med. and Immunology 3 (Aug. 28, 2003).

<sup>45</sup> Letter from Michael Carome, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Edward D. Miller, Dean and Chief Executive Officer, Johns Hopkins Med., Johns Hopkins Univ. Sch. of Med. et al. 3 (July 22, 2001) [hereinafter OHRP Letter to Johns Hopkins Univ. (7/22/2001)].

<sup>46</sup> Letter from Carol J. Weil, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Raymond Menard, Vice President, Administration, Ctr. for Molecular Med. and Immunology 1 (Nov. 5, 2003).

<sup>47</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to William Pinsky, Executive Vice President–Chief Academic Officer, Ochsner Clinical Found. 1 (May 13, 2002); Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Human Subject Prots., Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Benjamin Mojica, N.Y. City Dep’t of Health and Mental Hygiene (July 1, 2002).

to stop an institution from expending federal research funds on a particular study, in a specified department or school, or across the entire institution.<sup>48</sup> This is a powerful and dramatic penalty, and one that is rarely used. An instance did, however, show up in our sample: OHRP shut down all federally funded research at Hopkins following its audit.<sup>49</sup> The freeze lasted only three days, but was treated as a crisis by the institution.<sup>50</sup>

### B. Complaint Investigations

Table 5: Problems in OHRP Complaint Investigations (N=91)

Problem	Number of Investigations	Percentage
Faulty informed consent forms	47	52%
Deficiencies in IRB procedure	31	34%
Risky study	29	32%
Changes to study without approval	22	24%
Deficient reporting of adverse events	21	23%
Informed consent process	21	23%
Problems in subject recruitment	20	22%
Lack of IRB approval	16	18%
Privacy violations	12	13%
Improper waiver of informed consent	11	12%
Other problems	4	4%

1. *Problems Identified.*—Our review of OHRP letters in complaint-initiated investigations identified 235 problems in 91 matters. The average number of deficiency-types identified per investigation was 2.58, with a range of 0–8. The mode was 2. The most common problem, identified in 47 studies, was the wording of informed consent documents. Almost half the cases involved forms that OHRP felt simply ignored or at least touched too lightly on the issue of study risks. There was no suggestion in most of these cases that there were significant risks associated with the study, or

<sup>48</sup> 45 C.F.R. § 46.123 (2005).

<sup>49</sup> OHRP Letter to Johns Hopkins Univ. (7/19/2001), *supra* note 25, at 10. During the shut-down, Hopkins was required to perform a thorough review of its system and its problems, and to enact a variety of training and procedural steps to come back into compliance. OHRP Letter to Johns Hopkins Univ. (7/22/2001), *supra* note 45, at 2.

<sup>50</sup> Gina Kolata, *Johns Hopkins Death Brings Halt to U.S.-Financed Human Studies*, N.Y. TIMES, July 20, 2001, at A1 (“Hopkins officials reacted with outrage to the suspension of research, issuing a statement calling the action ‘unwarranted, unnecessary, paralyzing and precipitous’ and ‘an extreme example of regulatory excess.’ They pointed out that the suspension could have ‘potentially devastating’ effects, stopping studies that included cancer patients receiving experimental drugs.”).

that significant risks had been obscured in a way that might have enticed subjects to undergo a dangerous procedure under false pretenses. In several cases, however, OHRP determined that the form had omitted specific known and serious risks. In one case, the informed consent document for a study “failed to include an adequate description of the reasonably foreseeable risks of veno-occlusive disease (VOD) of the liver and its potential complications, including liver failure and death, known to be associated with the VAC drug regimen.”<sup>51</sup> In some cases, the OHRP found that serious risks had been disclosed to the subject, but not via the informed consent document. More often, the omitted risk was remote, such as a cancer risk associated with an approved drug that is listed on the drug’s FDA label and in the Physician’s Desk Reference.<sup>52</sup> In sixteen matters, OHRP determined that the consent form did not provide enough information about the study procedures, purposes or other details apart from the risks or discomforts. In principle, this sort of information is necessary to allow a potential subject to weigh the personal and social benefits of participation against both the risks and the burden of the study procedures.<sup>53</sup>

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<sup>51</sup> See Letter from Robert J. Meyer, Compliance Oversight Dir., Div. of Compliance Oversight, Office for Human Research Prots., to William A. Peck, Executive Vice Chancellor for Med. Affairs and Dean, Washington Univ. Sch. of Med. 2 (Jan. 7, 2003). The trial was testing a medication for Rhabdomyosarcoma, an often fatal childhood cancer. The OHRP cleared the investigators of allegations they “were unaware of previously reported cases of VOD, some of which resulted in subject death in the above-referenced research, and as a result failed to recognize and diagnose in a timely manner the development of VOD in a subject (DR) who subsequently died from complications related to this disorder.” *Id.* at 3.

<sup>52</sup> Letter from Leslie K. Ball, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Wyatt R. Hume, Executive Vice Chancellor, Univ. of Cal.–L.A. 3 (Mar. 19, 2002) [hereinafter OHRP Letter to UCLA (3/19/2002)].

<sup>53</sup> For example, in one letter, OHRP writes:

The following sentence from the section entitled, “Why Is This Study Being Done?” purports to explain the purpose of the research: “The purpose of this research study is to learn if a radioactive substance, injected around the tumor during surgery, will flow accurately to any malignant (cancerous) lymph nodes.” OHRP notes that in your response dated March 30, 2004, you propose to change the phrase “flow accurately” to “go to.” However, the revised paragraph still does not explain why the researchers want to learn if a radioactive substance will flow to the malignant lymph nodes. In particular, it does not explain why a radioactive substance is being used or why this procedure would be important to the care of individuals with lung cancer.

Letter from Karena Cooper, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Leopold G. Selker, Senior Vice President, Evanston Nw. Healthcare Research Inst. 2 (Apr. 20, 2004).

Overly complex language was the problem in six matters.<sup>54</sup> In some tension with its effort to simplify and shorten forms is OHRP's insistence that consent forms contain several stanzas of boilerplate it has interpreted the regulations to require.<sup>55</sup> This deficiency, which includes the failure to explicitly state that participation is voluntary, was identified in six cases. Rounding out this category were five matters in which the forms were deemed to contain forbidden exculpatory language (such as waivers of rights) and six complaints that were found to be unsubstantiated.

In 23% of the studies, OHRP was investigating whether the process of obtaining informed consent had been proper, or had been conducted at all. This category included a few cases in which institutional records did not contain clear documentation that consent forms had been approved and used.<sup>56</sup> It also included a number of cases in which investigators had not identified what they were doing as research, and so had not obtained IRB approval or deployed IRB-approved consent forms. In one case, for example, data originally collected for clinical purposes appeared later in scientific publications. OHRP found that the investigators should have submitted their planned research to the IRB and that use of the data brought their work within the definition of research requiring IRB approval.<sup>57</sup> Other cases involved the tardy presentation or completion of consent forms. In some instances, the researchers did not seek consent until after patients had been screened for eligibility, a step which the OHRP regards as part of the research process.<sup>58</sup> Eleven cases concerned allegations that the IRB had improperly applied the regulations governing waiver of informed consent or

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<sup>54</sup> The letters in these cases involve line-editing by regulators that could well be described as obsessive regulatory interference at its worst. *See, e.g., id.*; Letter from Kristina C Borrer, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Michael M. Gottesman, Deputy Dir. for Intramural Research, Nat'l Insts. of Health 1-3 (Mar. 17, 2003). In OHRP's defense, however, is a study finding that OHRP oversight activities were associated with a significant improvement in the readability of an institution's consent forms. *See* M.K. Paasche-Orlow, H.A. Taylor & F.L. Brancati, *Readability Standards for Informed-Consent Forms as Compared with Actual Readability*, 348 NEW ENGL. J. MED. 721, 724 (2003).

<sup>55</sup> *See* C.F.R. § 46.116(a)(8) (2003).

<sup>56</sup> *See, e.g.*, Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Fawwaz T. Ulaby, Vice President for Research, Univ. of Mich.—Ann Arbor 2 (Sept. 16, 2002).

<sup>57</sup> Letter from Leslie K. Ball, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Judith K. Argon, Vice President, Research Administration, The Children's Hosp. of Phila., The Joseph Stokes, Jr., Research Inst., Abramson Pediatric Research Ctr. 4 (Feb. 13, 2003); *see also* Letter from Kristina C Borrer, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Michael J. Klag, Vice Dean for Clinical Investigation, Johns Hopkins University School of Medicine (Oct. 23, 2003) (study completed and results published without ever undergoing IRB review).

<sup>58</sup> Letter from Leslie K. Ball, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Winfred M. Phillips, Vice President for Research, Univ. of Fla. 5-6 (Sept. 4, 2002) [hereinafter OHRP Letter to Univ. of Fla. (9/4/2002)]; OHRP Letter to UCLA (3/19/2002), *supra* note 52, at 2.

substitute consent.<sup>59</sup> In six cases, OHRP found the allegation to be unsubstantiated or outside its jurisdiction.

The second most prevalent category of problem was IRB procedural deficiency. Allegations ranged from missing IRB meeting minutes (6 cases) through lack of proper written internal operating procedures (7 cases) to a failure to ensure required review of continuing studies (7 cases).<sup>60</sup> In several cases, the OHRP concluded from its file review that the IRB lacked sufficient information about certain protocols to make an informed assessment.<sup>61</sup> Another common deficiency was the use of expedited reviews for studies that did not meet the regulatory criteria (5 cases) and lack of required diversity or other elements of IRB membership (5 cases).

In 29 cases, the OHRP alleged that the IRB had failed to minimize risk to human subjects. A breach of this rule does not necessarily entail a significant risk to the subjects, only a failure of the review process to identify risks that the researcher could have reduced. Almost two-thirds (18) of the complaints were found to be unsubstantiated, and 10 others involved findings that the IRB had not properly considered or documented its consideration of certain risks, though its ultimate approval of the protocol may have been correct. In one of these cases, a University of Chicago research project may have resulted in the death of a subject after researchers administered doses of pamidronate without adequately monitoring the subject's calcium levels.<sup>62</sup> OHRP found that the IRB properly reviewed the study

<sup>59</sup> See 45 C.F.R. §§ 116, 117 (2003).

<sup>60</sup> For example, OHRP provided the following guidance to one university:

Written IRB policies and procedures should provide a step-by-step description with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

- (a) The procedures which the IRB will follow for determining which projects require review more often than annually.
- (b) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.
- (c) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

OHRP strongly recommends that the IRB procedures be revised to include these operational details, if this has not already been done.

OHRP Letter to Univ. Cal.—Berkeley (12/3/2002), *supra* note 36, at 4.

<sup>61</sup> See, e.g., Letter from Karena Cooper, Compliance Oversight Coordinator, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Timothy F. Hawkins, Vice President, Clinical Serv., Baptist Hosp. of Miami, Inc. 3 (Apr. 23, 2004) (“[T]he IRB appeared to review only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.”).

<sup>62</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Mary Ellen Sheri-

and identified the risk, but failed to convey its concerns to the researcher. Two cases involved failure of the IRB to require a research design that minimized risks. In one case, OHRP judged the IRB-designated follow-up period for adverse events (30 days) too short to catch serious problems in a transplant study.<sup>63</sup> In a study of perchlorate exposure among healthy people,<sup>64</sup> the OHRP criticized the decision to randomize people to different dosage levels, rather than gradually increasing the dosage for all participants, because of the lack of data on the safety of higher doses.<sup>65</sup>

OHRP investigated 22 complaints that changes were made in studies without IRB approval. This is deemed both a failure of the investigator to comply with the rules and failure of the IRB to monitor. None of the cases involved serious increases in the risks to subjects, but unapproved changes are deemed problematic even if there is no indication of any increased risk to subjects because they obviate the IRB's screening function. So, for example, OHRP faulted researchers for failing to report and IRBs for failing to detect changes in adverse event reporting protocols,<sup>66</sup> or the addition of non-risky tests or procedures.<sup>67</sup> IRBs and institutions were criticized for failing to ensure that designated oversight meetings were held on the stipulated schedule.<sup>68</sup> One study fell afoul of OHRP on the basis of several changes: the use of an advertisement for subjects that was quite different from the version approved by the IRB; recruiting some subjects by telephone; hiring a contractor to provide technical support; and changing the study design from a randomized controlled trial to a two-by-two factorial design. OHRP noted "that, while these changes may not have increased risk to the participants, they were major changes to the protocol" and

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dan, Assoc. Vice President for Research, Univ. of Chi. 2 (Apr. 23, 2002). The patient was apparently elderly and the autopsy did not attribute the death to the study.

<sup>63</sup> Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to James H. Shore, Chancellor, Univ. of Colo., Health Sci. Ctr., & Joyce Cashman, Executive Vice President, Univ. of Colo. Hosp. 2 (Jan. 7, 2002).

<sup>64</sup> The original protocol summarized its purpose as follows: "Perchlorate has been found in very small amounts in the drinking water of certain communities in California, Nevada, and Arizona. This research study will investigate whether very small amounts of Perchlorate, such as encountered in ground water contamination, may change thyroid tests." Letter from Robert J. Meyer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to B. Lyn Behrens, President, Loma Linda Univ. et al. 2 (Nov. 14, 2002).

<sup>65</sup> *Id.* at 5. The OHRP's method would have reduced the risk to the higher dose subjects if a lower dose was found during the study to be dangerous.

<sup>66</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Zerababel M. Nyiira, Sec'y, Uganda Nat'l Council of Sci. and Technology, & Nelson K. Sewankambo, Uganda Nat'l Council of Sci. and Technology, Makerere Med. Sch. 4 (July 16, 2002).

<sup>67</sup> *See, e.g.*, Letter from Karena Cooper, Compliance Oversight Coordinator, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to John R. Sladek Jr., Vice Chancellor for Research, Univ. of Colo. Health Sci. Ctr. 3 (May 10, 2004).

<sup>68</sup> *See, e.g.*, OHRP Letter to Univ. of Fla. (9/4/2002), *supra* note 58, at 2.

needed to be reviewed under the Common Rule.<sup>69</sup> OHRP found four of the allegations in this category to be unsubstantiated.

OHRP investigated 21 cases of improper reporting of adverse events. Nine of these allegations were found to be unsubstantiated, but in others there were delays or failures to report adverse events including deaths. In none of these cases was the death found to be itself the result of research misconduct. Several of the cases reflect the bureaucratic intensity of the adverse event reporting process, which requires investigators to determine whether adverse events fit the regulatory definition, then to report to their IRB, and then to send reports to OHRP and, in many instances, the FDA.<sup>70</sup> The letter below, concerning a study conducted by NIH researchers, illustrates how a researcher can get into trouble in spite of apparently strenuous efforts to follow the rules and protect subjects:

OHRP finds that development of transfusion associated graft-versus-host disease and subsequent death of subject #4 in the research in 1999 represented an unanticipated problem involving risk to the subject and that this problem was not promptly reported to OHRP. OHRP acknowledges that this problem was promptly reported to the NIAID [National Institute of Allergies and Infectious Diseases] IRB, appropriate officials at the National Institutes of Health (NIH), and the Food and Drug Administration. Furthermore, OHRP acknowledges that all other subject[s] enrolled in the research were informed promptly of this newly identified risk of the research and were provided with medical bracelets alerting healthcare providers that these subjects should receive only irradiated blood cells if the subjects needed transfusions.<sup>71</sup>

Solving a problem is no defense against a charge of failure to report it. A U.S. principal investigator learned that a Norwegian collaborator had changed the study methodology without IRB approval and committed other flagrant breaches of the rules. She immediately undertook to work with the Dean of the Norwegian institution to replace the investigator and fix the problem, but failed to report it to the university and thence to OHRP. She was suspended as principal investigator until she had gone through what might reasonably be characterized as self-criticism and re-education.<sup>72</sup>

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<sup>69</sup> Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Maria H. Sjogren, Colonel, Med. Corps, Chief, Dep't of Clinical Investigation, Walter Reed Army Med. Ctr. 2 (Apr. 17, 2002).

<sup>70</sup> A "decision chart" on reporting provided as regulatory guidance by OHRP takes investigators and institutions through six steps to determine what reporting is required. See [http://www.hhs.gov/ohrp/policy/incidreport\\_ohrp.html](http://www.hhs.gov/ohrp/policy/incidreport_ohrp.html) (last visited Nov. 5, 2006).

<sup>71</sup> Letter from Michael A. Carome, Dir., Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Michael M. Gottesman, Deputy Dir. for Intramural Research, Nat'l Insts. of Health 2 (Feb. 27, 2002).

<sup>72</sup> Letter from Carol J. Weil, Compliance Oversight Coordinator, Div. of Human Subject Prots., Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Eugene P. Trani, President, Va. Commonwealth Univ. 2 (Apr. 8, 2003) ("The VCU IRB removed [the doctor] as PI at the VCU site and reinstated her only after it received her statement acknowledging her failure to notify VCU officials

Twelve investigations included allegations of insufficient privacy protection. None involved widespread release of information, nor a consequent subject injury. In seven cases, the OHRP was unable to substantiate the complaints. One investigation concerned the failure to observe the customary norms of placing files in a locked room, and encrypting or password protecting all computerized data.<sup>73</sup> Most of the others involved communications within a research team or between the team and a referring physician. These might be called “technical breaches” in so far as they involved transferring information at the wrong time (before consent forms were signed, for example) or to someone who, while generally privy to the information transferred, was not explicitly authorized to receive it from the research team. The most detailed account of a breach came in a study of recidivism among participants in a court-annexed adolescent substance abuse program that was administered in part by the investigator:

On at least one occasion, a print-out with the participation indication was transmitted to ASAP [Adolescent Substance Abuse Program]; it may have been available to court personnel. [The Researcher] has acknowledged that this was inappropriate, and he has removed the information from the database immediately upon learning of its existence.<sup>74</sup>

OHRP’s view of the matter seemed unaffected by the fact that the subjects’ participation in the substance abuse program—the only really sensitive information in the case—was already known to the court personnel who might have seen the record. Hence the only information that might be deemed confidential was that the subject was a research participant, which signified only that the participant’s recidivism would be monitored. It is not clear what makes this information “confidential,” other than that it is information about a person involved in research, nor that court personnel’s awareness that the program participant had agreed to be part of an evaluation would create any risk of harm to the subject. OHRP subsequently reported the resolution of the matter, a tighter privacy procedure: “OHRP acknowledges that the principal investigator has removed any research re-

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when she learned about the unauthorized research conducted on Norwegian Twin Registry subjects. [The Doctor] subsequently underwent PRIM&R/ARENA investigator training with emphasis on multinational studies and privacy issues.”)

<sup>73</sup> Letter from Rina Hakimian, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Raymond S. Greenberg, President, Med. Univ. of S.C. 1–2 (Apr. 21, 2004).

<sup>74</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Sadis Matalon, Acting Assoc. Provost for Research and Scholarship, Univ. of Ala.—Birmingham 3 (July 15, 2003). “The program was designed as an educational program for adolescents arrested on first-time drug or alcohol charges. The complainant’s daughter was required by the Jefferson County Family Court to participate in this non-research program.” *Id.* at 2.

lated information from any database which will be shared with court officials.<sup>75</sup>

Allegations of improper subject recruitment arose in 20 investigations, 9 of which were found to be unsubstantiated. Violations found included instances of ineligible subjects being included (sometimes overlapping with problems of approval of change in the protocol, so that the recruitment met the amended protocol requirements but the amendment had not been approved by the IRB). About half involved allegations that subjects had been pressured or coerced by, for example, being given too little time to read and reflect on the consent forms by physicians or other authority figures or care providers. These are the classic informed consent problems.<sup>76</sup> There were also instances of “unethical inducement” through offers of large amounts of money. Many ethicists, and apparently the OHRP, are not comfortable viewing study recruitment as an economic transaction and regard payment as problematic, especially payments to poor people.<sup>77</sup> Where money is offered, OHRP requires investigators to structure payments in a way that does not force participants to choose between exercising their right to withdraw at any time and receiving at least a pro-rata payment.<sup>78</sup>

One investigation, of an asthma study in rural China, implicated the growing practice of conducting clinical research in poor overseas regions. Apparently triggered by critical Chinese and then American news coverage,<sup>79</sup> the letters illustrate both the profound and trivial aspects of ethics regulation beyond US borders. On the trivial side, violations cited included changing the incentive from a flat payment of \$10 to reimbursement for meals, transport and lost wages (probably a similar amount) without IRB approval. On the profound side, the study raised the issue of whether the IRB sufficiently considered the ethics of testing drugs that would probably not be available to the tested population even if proven effective, and the

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<sup>75</sup> *Id.* at 3.

<sup>76</sup> See sources cited *supra* note 42.

<sup>77</sup> See Scott D. Halpern et al., *Empirical Assessment of Whether Moderate Payments Are Undue or Unjust Inducements for Participation in Clinical Trials*, 164 ARCH. INTERNAL MED. 801, 801 (2004) (citing commentary). Halpern found that increasing monetary inducements did not cloud potential subjects’ judgments about risk and seemed to influence wealthier people more than poor. *Id.* Others have criticized ethics boards’ “ill-informed attitudes” about payment issues. MARK ISRAEL, ETHICS AND THE GOVERNANCE OF CRIMINOLOGICAL RESEARCH IN AUSTRALIA viii, 15, 44 (2004).

<sup>78</sup> For example, a recruitment flyer promised \$1000 for completion of the study, in spite of the fact that the “IRB had asked the principal investigator to state in the informed consent document that the subjects would be compensated \$150 for each bronchoscopy, thereby reducing undue influence of offering large amounts of money for completing the trial.” Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Gregory W. Siskind, Assoc. Dean for Research and Sponsored Programs, Cornell Med. Ctr., & David P. Hajjar, Frank H.T. Rhodes Distinguished Professor and Dean, Cornell Med. Ctr. 10 (Apr. 4, 2002) [hereinafter OHRP Letter to Cornell Med. Ctr. (4/4/2002)].

<sup>79</sup> John Pomfret and Deborah Nelson, *An Isolated Region’s Genetic Mother Lode: Harvard-Led Study Mined DNA Riches Some Donors Say Promises Were Broken*, WASH. POST, Dec. 20, 2000, at A1.

broader potential for abusive manipulation of poor people in profit-driven medical research. Of further interest here was the OHRP's use of the *Belmont Report* as the substantive regulatory standard: "[W]henever research supported by public funds leads to the development of therapeutic devices and procedures," OHRP wrote, "justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research."<sup>80</sup> Although the Common Rule is supposed to foster consideration of fundamental principles like justice or autonomy, it is rare in the letters to find OHRP explicitly correcting an IRB's resolution of a difficult and disputed ethical question.<sup>81</sup>

OHRP again took on the role of ethical umpire in halting an NIH-funded Oregon Health and Science University study designed to determine whether mandatory drug testing of student athletes was an effective means of reducing teen drug abuse. The study entailed randomizing participating

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<sup>80</sup> Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to John H. Lichten, Dean for Administration and Finance, Harvard Sch. of Pub. Health 15 (Mar. 28, 2002) [hereinafter OHRP Letter to Harvard Sch. of Pub. Health (3/28/2002)].

<sup>81</sup> Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Keith A. Marcotte, Vice President for Research Administration, Brigham and Women's Hosp. (July 24, 2002); OHRP Letter to Harvard Sch. of Pub. Health (3/28/2002), *supra* note 80. On the issue of whether and under what circumstances trials in poor populations are ethical, compare Jay Dyckman, *The Myth of Informed Consent: An Analysis of the Doctrine of Informed Consent and Its (Mis)Application in HIV Experiments on Pregnant Women in Developing Countries*, 9 COLUM. J. GENDER & L. 91, 107 (1999), with Harold Varmus & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW ENG. J. MED. 1003 (1997).

Part of the dispute over the study turned on the risks of research in China that recruited families with more than one child:

The protocol "Genetics of Airway Responsiveness and Lung Function" required a family size of 4 or greater. This requirement does not appear to be consistent with the "one child family" rule of China. Although in their January 30, 2002 letter B&WH noted that the principal investigator indicated that the rule was relaxed in rural areas, the article by Susan Greenhalgh (Population & Development Review, 1986, 12(3): 491-515) provided by B&WH makes it clear that although the rules were relaxed for second children under very specific circumstances, "third children were not supposed to be allowed under any circumstances." OHRP is concerned that identification of families having 3 or more children participating in the research study could have placed them at risk in regard to this rule and that the IRB did not adequately consider this risk. B&WH stated that the average family size for protocol #94-06932 was 4.5, indicating that many families had at least 3 children.

Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep't of Health and Human Servs., to Keith A. Marcotte, Vice President for Research Administration, Brigham and Women's Hosp. (Mar. 28, 2002). Whether or not the policy was in fact being violated by the subjects, the OHRP did not explain why the authorities in China would have required study participation (as opposed to, say, school enrollment or health records or community-level informants), to identify families in violation. See Nicole M. Skalla, *China's One-Child Policy: Illegal Children and the Family Planning Law*, 30 BROOK. J. INT'L L. 329, 336-39 (2004) (describing implementation of policy). This is an example of pure speculation about a social risk emerging as a significant barrier to a study.

schools to either a mandatory testing or a no testing group. The investigators recruited the schools and the study paid for and performed the tests. Once a school entered the study, students were, in effect, automatically recruited to participate. Students at drug testing schools who refused testing were barred from athletics. Parents and school officials were to be informed of positive drug tests. The study was reviewed and approved by the responsible IRB.<sup>82</sup> School drug-testing programs were being implemented across the United States and had been upheld by state courts and ultimately the U.S. Supreme Court against constitutional privacy challenges.<sup>83</sup>

OHRP regarded a study that involved mandatory drug testing under these circumstances as inherently unethical and took the position that those who had designed and approved the study had simply got it wrong. “The particular nature of the study design,” it wrote, “may have prevented both the OHSU Institutional Review Board (IRB) and the investigators from clearly recognizing that the drug testing is an integral part of the study.”<sup>84</sup> It immediately suspended the research.

After several months, the university submitted a response contesting the OHSU’s allegations that the study was unduly coercive or that “mandatory drug testing of student athletes is an integral part of the design.”<sup>85</sup> The university proposed a number of corrective actions. These included an end to new enrollments in the study; having its IRB re-review the study to make sure the consent form clearly set out the goals of the research; and removing the researchers from any role in actually implementing the mandatory drug testing programs.<sup>86</sup> OHRP responded that:

because under the IRB-approved protocol (a) subjects are randomly assigned in groups (i.e., all student athletes at a particular school) to either mandatory drug testing or no mandatory drug testing; and (b) for student athletes at a school randomized to the mandatory drug testing intervention, continued participation in the school athletic programs is contingent upon participation in the major research intervention, OHRP finds that the proposed corrective actions fail to address the finding that the informed consent of the subjects is not

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<sup>82</sup> OHRP Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., U.S. Dep’t of Health and Human Servs., to Peter O. Kohler, President, Or. Health & Sci. Univ. 1–2 (Oct. 24, 2002) [hereinafter OHRP Letter to Univ. of Or. (10/24/2002)]. It appears that the investigators tried to obscure the fact that the testing programs were part of a research project, perhaps to increase verisimilitude. In any event, OHRP also had extensive objections to the consent forms and processes. For a critical account of the study and more details of its goals and methods, see Adil E. Shamoo & Jonathan D. Moreno, *Ethics of Research Involving Mandatory Drug Testing of High School Athletes in Oregon*, 4 AM. J. BIOETHICS 31 (2004).

<sup>83</sup> Bd. of Educ. of Indep. Sch. Dist. No. 92 of Pottawatomie County v. Earls, 536 U.S. 822 (2002); Weber v. Oakridge Sch. Dist. 76, 56 P.3d 504 (Or. Ct. App. 2002), *aff’d*, 69 P.3d 1233 (Or. 2003).

<sup>84</sup> OHRP Letter to Univ. of Or. (10/24/2002), *supra* note 82.

<sup>85</sup> Letter from Kristina C Borrer, Dir., Division of Compliance Oversight, Office for Human Research Prots., to Peter O. Kohler, President, Oregon Health & Science University (Apr. 17, 2003).

<sup>86</sup> *Id.*

being sought under circumstances that minimize the possibility of coercion or undue influence.

OHRP continued the suspension, rejecting another set of proposed remedies in January, 2004, but noting “that analysis of data that has been permanently stripped of all identifiers and can never be linked to identifiable private information would not be considered human subjects research and could continue under OHRP’s restriction.”<sup>87</sup> The moment of bureaucratic perfection arrived in May 2004, when OHRP lifted the suspension on the research on the ground that the project had been closed.<sup>88</sup>

Reasonable minds can differ vigorously about the morality of testing students for drugs, but presumably reasonable minds might form more reasonable judgments given data on the costs and benefits of the intervention, which is going on throughout the country whether it is studied or not. What is striking here is how the values of OHRP (or its staff) emerge in this case from behind the veil of the more typical enforcement of paperwork and procedures, and how it imposed those values on IRBs (ordinarily set up as the best judge of community norms) and investigators.<sup>89</sup>

The complaint letters almost never raised the question of whether someone had actually been harmed by the reported defaults. In one letter, OHRP noted that the institution itself had retained a specialist to review patient records, and the specialist had determined that an unauthorized procedure had not caused physical harm to any of the patients.<sup>90</sup>

2. *Remedial Measures.*—As in the audits, the most common response to a complaint, substantiated or not, was to add a new procedure or form.<sup>91</sup>

<sup>87</sup> Letter from Kristina C Borrer, Dir., Div. of Compliance Oversight, Office for Human Research Prots., to Peter O. Kohler, President, Or. Health & Sci. Univ. (Jan. 15, 2004).

<sup>88</sup> Letter from Kristina C Borrer, Dir., Div. of Compliance Oversight, Office for Human Research Prots., to Peter O. Kohler, President, Or. Health & Sci. Univ. (May 28, 2004).

<sup>89</sup> The potential role of ethics oversight authorities to act as censors of controversial research has been raised by commentators, see Philip Hamburger, *The New Censorship: Institutional Review Boards*, 2004 SUP. CT. REV. 271 (2005), and validated by experiment, see Stephen J. Ceci, Douglas Peters & Jonathan Plotkin, *Human Subjects Review, Personal Values, and the Regulation of Social Science Research*, 40 AM. PSYCHOLOGIST 994 (1985). In the case of the Oregon study, the former head of OHRP defended the agency, insisting that it was not making a value judgment about drug testing, but enforcing federal law banning coerced participation in research. Greg Koski, *Drug-Testing Research in High School Students: Is There a Will or A Way?*, 4 AM. J. BIOETHICS 33 (2004).

<sup>90</sup> Letter from Leslie K. Ball, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Robert O. Webster, Assoc. Provost for Research Administration, St. Louis Univ. Health Scis. Ctr. (July 29, 2002).

<sup>91</sup> See, e.g., Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Mary Ellen Sheridan, Assoc. Vice President for Research, Univ. of Chi. (Apr. 23, 2002) [hereinafter OHRP Letter to Univ. Chi. (4/23/02)] (“OHRP acknowledges the corrective actions taken by UC to address the above finding including . . . the development of a reviewer’s checklist of assure that the requirements for approval of research involving children are addressed by the IRB.”); Letter from Leslie K. Ball, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Winfred M. Phillips, Vice Presi-

Institutions also frequently responded by putting researchers and IRB members through extra training.<sup>92</sup> The third most common response was to change informed consent documents, either by using a new template institution-wide or changing the wording in a specific document.<sup>93</sup>

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dent for Research, Univ. of Fla. (Sept. 4, 2002) (“The UF IRB has modified its continuing review report form to require that if such a committee has been listed in the protocol, the principal investigator should provide information on all oversight committee reviews to the IRB . . . .”); Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Human Subject Prots., Office for Human Research Prots., to Steven G. Ullmann, Vice Provost for Faculty Affairs, Univ. Admin., Univ. of Miami (Aug. 5, 2002) (“OHRP acknowledges the UM IRB’s statement that their reporting requirements should be broader and should require reporting of DSMB reports. The protocol application is being revised to solicit information about DSMBs, and the continuing review report form is being revised to include specific information about DSMB activities.”); Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Fawwaz T. Ulaby, Vice President for Research, Univ. of Mich. (Sept. 15, 2003) (“In an effort to enhance its system for protection of human subjects, UM has implemented the following changes: (i) Established a University-wide Human Research Coordinating Council . . . . (iv) Established a new Office of Research Compliance Review . . . . (v) Developed a comprehensive electronic administration and documents processing system . . . .”).

<sup>92</sup> See, e.g., Letter from Leslie K. Ball, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Alan H. Teramura, Senior Vice President for Research, Office of Research Servs., Univ. of Haw. (Aug. 5, 2002) (“OHRP acknowledges . . . that UH initiated a comprehensive restructuring of its human subjects research review and oversight system that has included additional training for UH IRB members and investigators . . . .”); Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Randy P. Juhl, Vice Chancellor for Research Conduct and Compliance, Univ. of Pittsburgh, and Susan Burkett, Assoc. Provost for Research & Academic Admin., Carnegie Mellon Univ. (May 3, 2004) (“OHRP has determined that the corrective actions summarized below appropriately address the issues raised . . . . U Pitt and CMU IRBs are enhancing their training for IRB members and researchers on confidentiality issues to help prevent such an incident in the future.”); Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Mary Ellen Sheridan, Assoc. Vice President for Research, Univ. Research Admin, Univ. of Chi. (Apr. 23, 2002) (“OHRP acknowledges the corrective actions taken by UC to address the above finding including (i) retraining IRB staff and IRB chairs on the process for summarizing and assuring that investigators have responded to all issues raised by the IRB . . . .”).

<sup>93</sup> See, e.g., OHRP Letter to Cornell Univ. Medical Center (4/4/2002), *supra* note 78 (requiring IC template forms to include “a statement that the study involves research”); Letter from Karena Cooper, Compliance Oversight Coordinator, Office for Human Research Prots., to Leopold G. Selker, Senior Vice President, Evanston Northwestern Healthcare Research Inst. (Apr. 20, 2004) (stating that standard consent form must include statements identifying “any procedures which are experimental”); Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Thomas Q. Morris, Vice President, Columbia Univ. Health Scis. (Dec. 2, 2002) (consent forms must be changed to include all “the reasonably foreseeable risks and discomforts of the subject’s participation in the research . . . including the ‘risk of death from coffee enemas’”); Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Aram V. Chobanian, Med. Campus Provost, Boston Univ. Med. Ctr. (Apr. 10, 2002) (OHRP required revisions to IC template adding “a statement that participation is voluntary.”).

Table 6: Responses To OHRP Complaint Investigation Determinations (N=91)

Response	Number of Investigations with the Response	Percentage
New procedure	35	39%
Training	32	36%
New informed consent documents	29	32%
Study changed/stopped	10	11%
Staff change	10	11%
New IRB members	8	9%
Researcher excluded	5	6%
Tightened security	4	4%
Other	3	3%

None of the complaints led to an institution-wide suspension of research. In ten cases, a particular study was temporarily or permanently stopped, and in five a researcher was suspended from conducting some or all research at the institution.<sup>94</sup> In a few of the cases, it was not clear from the letter whether the study had ended or ceased enrollment of new subjects in response to OHRP inquiries, or whether it had simply reached its anticipated endpoint. As would be expected, this category of responses included some of the more serious or disputed cases. In one case, the adolescent substance abuse evaluation described above,<sup>95</sup> the researcher included in his study data concerning a person ordered to participate in the intervention but who had not enrolled in the research. The researcher was suspended for six months.<sup>96</sup> In another, the case of the errant Norwegian collaborator,<sup>97</sup> the Norwegian site was suspended pending the issuance of a valid single-project assurance.<sup>98</sup> The most apparently disputatious case was the Oregon

<sup>94</sup> For example, in the case of the Harvard China asthma research, the university suspended the investigator's research projects and suspended him from applying for new research projects as a principal investigator. Harvard also "implemented a plan to monitor Dr. [X]'s ongoing research involving human subjects, involving oversight of data management systems by an appointed data monitor, and has plans to conduct consent monitoring at international sites." Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots, to John H. Lichten, Dean for Admin. & Fin., Harvard Sch. of Pub. Health (July 24, 2002).

<sup>95</sup> See *supra* notes 74–75 and accompanying text.

<sup>96</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Sadis Matalon, Acting Assoc. Provost for Research & Scholarship, Univ. of Ala. at Birmingham (July 15, 2003).

<sup>97</sup> See *supra* note 72 and accompanying text.

<sup>98</sup> Letter from Carol J. Weil, Compliance Oversight Coordinator, Div. of Human Subject Prots., Office for Human Research Prots., to Eugene P. Trani, President, Va. Commonwealth Univ. (Apr. 8, 2003). A "single-project assurance" is an agreement between an institution and OHRP to govern oversight of a single study.

high school drug testing study, which the OHRP halted. In ten cases, the institution made a staff change as a result of the letter, which involved either terminating a staff member (mostly administrative employees) or adding another staff member to help oversee research protocol. For example, after one complaint, the researcher running the study hired a new lab coordinator with human subjects compliance experience.<sup>99</sup>

In the most serious sanction, a researcher's projects were terminated, he was barred from serving as principal investigator for two years, and future reinstatement was subject to the requirements that he: "(i) undergo face-to-face good research practices training; (ii) have ongoing departmental supervision; (iii) develop a revised recordkeeping system; and (iv) be subject to ongoing auditing of any future human subjects research."<sup>100</sup> Despite the extreme sanction, the nature of the investigator's default on paper was not substantially more serious than in other letters reviewed. These included: "OHRP finds that the Institutional Review Board (IRB)-approved informed consent document failed to describe (a) the pain and discomfort associated with injection of local anesthetic; and (b) sudden sharp pain that may occur when the nerve is severed even if local anesthesia is used during the sural nerve biopsy."<sup>101</sup> The OHRP also found that the researcher had changed the protocol without IRB approval by including healthy controls and by offering remuneration to the subjects.<sup>102</sup>

### III. DISCUSSION

#### A. OHRP, Ethics, and Bureaucracy

In some respects, OHRP's enforcement letters show a system that is working reasonably well. There are real risks in research. In biomedical studies, particularly clinical studies involving already sick subjects, the risks include physical injury and death.<sup>103</sup> Very few researchers investi-

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<sup>99</sup> Letter from Kristina C Borrer, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Paul Levy, President, Beth Israel Deaconess Med. Ctr. (Apr. 30, 2002).

<sup>100</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Thomas J. Rosol, Interim Vice President for Research, Office of Research, Ohio State Univ. (Jan. 12, 2004).

<sup>101</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to C. Bradley Moore, Vice President for Research, Office of Research, Ohio State Univ. (Dec. 4, 2002).

<sup>102</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator, Div. of Compliance Oversight, Office for Human Research Prots., to Thomas J. Rosol, Interim Vice President for Research, Office of Research, Ohio State Univ. (Sept. 29, 2003).

<sup>103</sup> One study found that 46% of studies involved said some subjects or controls were seeking or receiving clinical care, and 47% of these involved serious conditions; 16% of all protocols involved someone who was terminal, had a medical emergency, or for some other reason had an attenuated ability to comprehend the issues of research participation. BELL, *supra* note 21, at 22.

gated by OHRP appear to have deliberately broken or disregarded the rules.<sup>104</sup> Very, very few researchers conducted their studies in a way that endangered their subjects. The rate of serious problems—cases in which subjects were put at serious risk or suffered harm—was low, especially when the denominator is not the number of letters, complaints, or audits but the far greater number of studies going on in this period.<sup>105</sup> Most of the violations uncovered involved the failure to document something that may actually have been done, or a failure to do something that, while required by the regulations, does not appear to have exposed anyone to any harm or even put anyone at any appreciable risk. Most investigators and institutions were trying to comply, and seemed to appreciate the importance of protecting human subjects.<sup>106</sup>

In doing its work, the agency seems to conform to the model of “responsive regulation” articulated by leading scholars on regulation.<sup>107</sup> (For a graphical depiction of the OHRP enforcement pyramid, see Figure 1, below.)<sup>108</sup> OHRP begins with the assumption that institutions are trying to comply with the rules. It devotes considerable resources to education and formal and informal regulatory guidance aimed at facilitating compliance. When it gets wind of a possible breach, it proceeds gently in tit-for-tat movements up and down the “regulatory pyramid.” First, there is informal information-sharing to determine whether the complaint has any basis. The OHRP works with the institution, and at first relies on the institution to investigate and report back. In the vast majority of instances, OHRP is satis-

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<sup>104</sup> Many of the others defaulters appear to have committed their breaches out of confusion or impatience with red tape. See Burris & Moss, *supra* note 35.

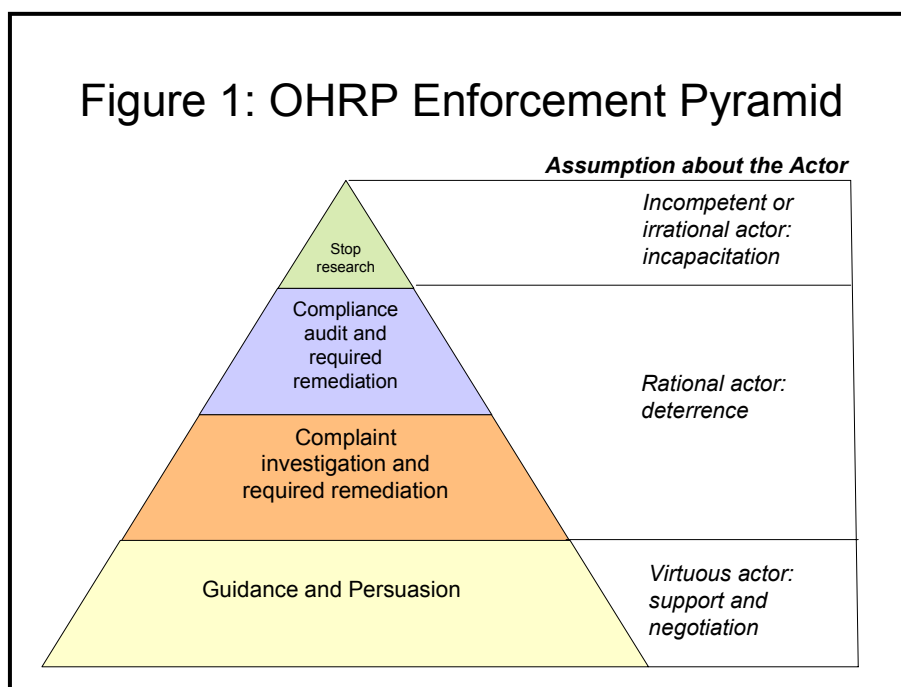
<sup>105</sup> It has been estimated that there are 16,000 to 20,000 research studies in the U.S. each year, and that as many as 2 million people will participate in medical experiments in a typical year. See Richard Saver, *Medical Research and Intangible Harm*, 74 UNIV. CIN. L. REV. 941, 944 (2006). The rate of harms uncovered by OHRP is consistent with the limited empirical literature on harm to subjects. See Roxanna Alcaraz, Elizabeth A. Klonoff & Hope Landrine, *The Effects on Children of Participating in Studies of Minors' Access to Tobacco*, 26 PREVENTIVE MED. 236 (1997); BELL, *supra* note 21; Robert Bortolussi & Diann Nicholson, *Auditing of Clinical Research Ethics in a Children's and Women's Academic Hospital*, 25 CLINICAL & INVESTIGATIVE MED. 83 (2002); Philippe. V. Cardon, F. William Dommel & Robert Trumble, *Injuries to Research Subjects: A Survey of Investigators*, 295 NEW ENG. J. MED. 650 (1976); see also Elizabeth Horstmann et al., *Risks and Benefits of Phase I Oncology Trials, 1991 Through 2002*, 352 NEW ENG. J. MED. 895 (2005) (estimating that up to 0.49% of terminal cancer patients in Phase I trials die from toxic events in the research).

<sup>106</sup> We share the view of many that the bioethics movement and the Common Rule were important drivers (and mirrors) of a social change that led to far greater sensitivity to the welfare of subjects than was the norm in, say, 1955 or 1960. See Burris & Moss, *supra* note 35; Sydney A. Halpern, *Constructing Moral Boundaries: Public Discourse on Human Experimentation in Twentieth-Century America*, in BIOETHICS IN SOC. CONTEXT 69 (Barry Hoffmaster ed., Temple Univ. Press 2001); David J. Rothman, *Ethics and Human Experimentation: Henry Beecher Revisited*, 317 NEW ENG. J. MED. 1195 (1987).

<sup>107</sup> The concept of “responsive regulation” is associated with the work of Ian Ayres and John Braithwaite. See IAN AYRES & JOHN BRAITHWAITE, *RESPONSIVE REGULATION: TRANSCENDING THE DEREGULATION DEBATE* (1992).

<sup>108</sup> See *infra* p. 672.

fied it is dealing with a “virtuous actor” and uses no more than persuasion and information to maintain compliance. When OHRP detects an institution behaving more in the vein of a “rational actor”—only as good as it needs to be to avoid paying more in penalties than compliance would cost—OHRP escalates slowly. It can open a formal investigation, but even here it continues to rely on the institution itself to collect information and propose solutions. Only rarely does it emphasize its deterrent capacity by conducting a general audit or site visit. Its heaviest sanction—shutting down some or all research—is hardly ever deployed.



(Adapted from AYRES & BRAITHWAITE, *supra* note 107; BRAITHWAITE, HEALY & DWAN, *infra* note 150.)

But a review of OHRP enforcement letters also indicates no substantial change since NBAC complained about OHRP’s counterproductive focus on paper compliance.<sup>109</sup> Our study confirms that the agency continues to nit-pick consent forms, depend upon (and demand) extensive documentation of compliance activities, and find the remedy for most problems to be “more”—review of studies, internal monitoring procedures, education, forms. We suspect OHRP’s oversight is continuing to promote a culture of red tape rather than a culture of ethics, and meeting the demands of OHRP entails more and more institutional resources being devoted to smaller and

<sup>109</sup> See *supra* text accompanying note 5.

smaller gains for human subject protection.<sup>110</sup> In service of its reading of the Common Rule, OHRP demands that most or all studies get some kind of advance review; that *all* changes, no matter how trivial, be approved by an IRB; that the IRB meaningfully monitor on-going research; and that consent forms be both readable and larded with boilerplate. All of those requirements expand bureaucratic oversight and multiply file cabinets. Even the head of OHRP himself has expressed frustration with the institutional response to its efforts:

We find that institutions treat guidance as regulations, and institute new rules internally that are burdensome and not required, . . . like unnecessary adverse event reports. . . . The other example is what has happened to consent forms. They used to be 2–3 pages that people may have read, and now they are 20–30. I’ve seen them over a hundred pages long and they are not protecting subjects. That’s a burden that we don’t create, but the institutions trying to escape liability.<sup>111</sup>

### B. Regulatory Paradox

Thus we come to paradox. OHRP is performing well, but the regulatory system is not. More broadly, a system invented to foster individual and institutional commitments to serious philosophical deliberation and ethical concern for subjects is growing into just another set of federal regulations. What’s going wrong? At least three explanations emerge from our consideration of OHRP’s enforcement process: poor rules, poor tools, and over-deterrence.

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<sup>110</sup> Criticism of the growth of the IRB system has been steady over the years, though few studies have investigated how the regulatory regime actually works. See PANEL ON IRBS, *supra* note 7; THE CENTER FOR ADVANCED STUDY, IMPROVING THE SYSTEM FOR PROTECTING HUMAN SUBJECTS: COUNTERACTING IRB “MISSION CREEP” (2005); Charles Warlow, *Over-Regulation of Clinical Research: A Threat to Public Health*, 5 CLINICAL MED. 33 (2005). The few studies that have been conducted show that compliance activities cost investigators and institutions a considerable amount of time and money. Burris & Moss, *supra* note 35, at 44–45; Bell, *supra* note 21, at 40–54; Keith Humphreys, Jodie Trafton & Todd H. Wagner, *The Cost of Institutional Review Board Procedures in Multicenter Observational Research*, 139 ANNALS OF INTERNAL MED. 77 (2003); Todd H. Wagner et al., *The Cost of Operating Institutional Review Boards (IRBs) in the VA*, 78 ACAD. MED. 638 (2003). The rules may also be stifling important research for questionable reasons. Ceci et al., *supra* note 89; Tu et al., *supra* note 9; cf. Sarah M. Greene et al., *Impact of IRB Requirements on a Multicenter Survey of Prophylactic Mastectomy Outcomes*, 16 ANNALS OF EPIDEMIOLOGY 275, 276–78 (2006); Craig D. Newgard et al., *Institutional Variability in a Minimal Risk, Population-Based Study: Recognizing Policy Barriers to Health Services Research*, 40 HEALTH SERVS. RES. 1247 (2005). Furthermore, it may deter researchers from pursuing work in regulatory hot-spots such as vulnerable populations. See Burris & Moss, *supra* note 35, at 52; cf. ISRAEL, *supra* note 77, at 38–40 (discussing problem with Australian IRBs and protection of vulnerable populations). Researchers support protecting human research subjects, but they resent what they regard as silly or counterproductive requirements in areas like informed consent or research involving purely hypothetical risks. See Liza Dawson & Nancy E. Kass, *Views of US Researchers About Informed Consent in International Collaborative Research*, 61 SOC. SCI. & MED. 1211 (2005).

<sup>111</sup> Interview with Bernard Schwetz, *supra* note 12.

1. *Poor Rules.*—Part of the problem is the nature of the standards the OHRP enforces. The Common Rule draws on two classes of “rules”: ethical principles, which define what is proper to do, and the regulations themselves, which “implement” the principles by reducing them to a series of requirements with which a given IRB can document compliance.<sup>112</sup> The desired outcome of this regulatory effort is behavior that complies with ethical principles, but that is really quite difficult to define in a wide range of normal cases—hence the bioethics profession and its extensive literature on matters like conflict of interest, coercion, and distributive justice, for example.<sup>113</sup> Leaving aside the thankfully rare cases of extreme conduct, reasonable minds can and do generally differ on the requirements of justice, beneficence, and autonomy. These are inherently indeterminate concepts that within broad ranges of socially constructed agreement cannot dictate a universally acceptable course of conduct.<sup>114</sup> The Common Rule gets around this indeterminacy—and produces the possibility of a “right answer”—through procedure, by requiring the IRB to deliberate and empowering it to define what is ethical or not in a particular case. Variance between IRBs is shielded rhetorically by the premise that every IRB deploys special, local knowledge. The system produces the possibility of right or wrong answers, but those answers are not right or wrong based on ethical principles; rather, they are right or wrong with respect to the implementation steps set forth in the regulations. An institution cannot, under normal circumstances, be faulted for failing sufficiently to appreciate and protect the autonomy of the subject. It can be faulted for failing to require the investigator to include a boilerplate statement on the consent form reminding the subject that she may withdraw from the study at any time without penalty or other negative consequences. The person who wrote or the IRB that approved that consent

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<sup>112</sup> The HHS regulations are intended to implement the basic ethical principles governing the conduct of human subjects research. These ethical principles are set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1978) [hereinafter BELMONT REPORT].

<sup>113</sup> See, e.g., S.S. COUGHLIN, *ETHICS IN EPIDEMIOLOGY AND CLINICAL RESEARCH: ANNOTATED READINGS* (Stephen S. Coughlin ed., 1995); Carl H. Coleman, *Duties to Subjects in Clinical Research*, 58 VAND. L. REV. 387 (2005); Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 NEW ENG. J. MED. 847 (1997); Robert Gatter, *Human Subjects Research and Conflicts of Interest: Walking the Talk of Trust in Human Subjects Research: The Challenge of Regulating Financial Conflicts of Interest*, 52 EMORY L.J. 327 (2003); Sheldon Krimsky, *The Funding Effect in Science and Its Implications for the Judiciary*, 13 J.L. & POL'Y 43 (2005); Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW ENG. J. MED. 853 (1997).

<sup>114</sup> For extended discussion of indeterminacy in American law, see, for example, Jules L. Coleman & Brian Leiter, *Determinacy, Objectivity, and Authority*, 142 U. PA. L. REV. 549, 578 (1993); Michael C. Dorf, *Legal Indeterminacy and Institutional Design*, 78 N.Y.U. L. REV. 875, 928 (2003); Joseph W. Singer, *The Player and the Cards: Nihilism and Legal Theory*, 94 YALE L.J. 1 (1984).

form could well have considered autonomy carefully and decided that language about withdrawal was not important to this particular study and detracted from the comprehensibility of the form. This, however, would be no defense to the charge that the consent form was defective by reference to the regulations. Given indeterminacy and oversight, the institution's compliance is measured not by the quality of its ethical deliberations but the review steps and decisions it documents.

The *Belmont Report* itself warned that “[t]hese principles cannot always be applied so as to resolve beyond dispute particular ethical problems,”<sup>115</sup> and the empirical literature consistently supports the Belmont Commission's intuition: IRBs looking at the same studies typically disagree on what is good and bad about them, and what changes ethics require.<sup>116</sup> There is no mechanism in the regulatory system for developing a transparent “common law” of ethics, and though some have called for making the system more court-like (with written opinions and appellate review),<sup>117</sup> such suggestions only highlight how far the IRB mission has crept since the institution was created as a form of heightened peer review fifty years ago.

To the extent that the Common Rule attempts to instantiate ethical principles in specific standards, it uses some quite difficult concepts. A key question in determining how a protocol will be reviewed and the sort of consent process required is whether the study poses “minimal risk” or “greater than minimal risk.” Findings on this point will often differ because IRBs typically lack objective data on risk, and risk assessment tends to be driven by other factors. There is evidence that IRBs have trouble applying these concepts correctly and consistently.<sup>118</sup> The OHRP letters do sometimes present cases in which the OHRP finds a substantive error of risk assessment, but only in cases where a particular risk (such as a drug side-

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<sup>115</sup> BELMONT REPORT, *supra* note 112, at 2. It went on: “The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.” *Id.*

<sup>116</sup> See, e.g., William Burman et al., *The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium*, 24 CONTROLLED CLINICAL TRIALS 245 (2003); Greene et al., *supra* note 110; J. Mark Hirshon et al., *Variability in Institutional Review Board Assessment of Minimal-Risk Research*, 9 ACAD. EMERGENCY MED. 1417 (2002); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 J. AM. MED. ASS'N 360 (2003); Newgard et al., *supra* note 110; Henry Silverman, Sara Chandros Hull & Jeremy Sugarman, *Variability Among Institutional Review Boards' Decisions Within the Context of a Multicenter Trial*, 29 CRITICAL CARE MED. 235 (2001); Thomas O. Stair et al., *Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial*, 8 ACAD. EMERGENCY MED. 636 (2001).

<sup>117</sup> Carl H. Coleman, *Rationalizing Risk Assessment in Human Subject Research*, 46 ARIZ. L. REV. 1, 49–51 (2004).

<sup>118</sup> See, e.g., Hirshon et al., *supra* note 116; McWilliams et al., *supra* note 116; Seema Shah et al., *How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research?*, 291 J. AM. MED. ASS'N 476 (2004).

effect identified in the FDA label) is already known. Apart from adopting far more rigorous and expensive evaluative methods, OHRP cannot routinely measure whether, on average let alone in all cases, IRBs are accurately applying the risk standards. For both institutions and the OHRP, compliance typically is shown by the IRB discussing the risks and invoking the correct standards at the correct points of review. Whether risks to subjects really were kept to a minimum is rarely determined or determinable by an IRB or OHRP.

Aside from the indeterminacy and difficulties of the rules themselves, a second set of problems arises from the application of the same rules to all research, regardless of the field, methodology or nature and degree of risks posed to subjects. The OHRP recognizes that IRBs are overworked, but the agency's efforts conspire relentlessly to ensure that institutions cannot budget their resources according to likely risks. From the OHRP's standpoint, prior review of an observational study of exercise habits of healthy people is as important as reviewing a study of new cancer treatment for the sick; a change in the wording of a survey about television preferences may get the same review and approval process as a change in drug dosage in a clinical trial. Despite amendments to the Common Rule intended to exempt most low risk social and behavioral research, OHRP assurances negotiated with universities commonly include promises from the institution to review research that is exempt from the regulations.<sup>119</sup> One study showed that expedited review, another regulatory innovation intended to allow faster processing of low risk research, actually took longer than regular IRB review.<sup>120</sup> Some institutions are now dealing with the crush of review by contracting with what might be called ethics factories, external companies employing full-time IRBs to perform the review function off-site at an industrial scale and pace.<sup>121</sup> One wonders how early proponents of ethics in research would have reacted to the "outsourcing" of the institutional conscience. Certainly this phenomenon speaks volumes about the gap between the *Belmont Report's* ideal of ethical deliberation and the reality of Common Rule compliance.

2. *Poor Tools.*—Bureaucratization of research also has something to do with the tools that OHRP and institutions deploy to oversee research and assure respect for subjects. Because OHRP cannot, as it is presently consti-

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<sup>119</sup> Revisions promulgated in 1981 introduced five categories of exempt research. The head of the agency that drafted the regulations estimated that 80% of the social and behavioral research it sponsored would be exempt. PANEL ON IRBS, *supra* note 7, at 71–73. The 1981 revision also allowed "expedited" review for studies posing "no more than minimal risk." These mechanisms to dispense with any, or with full, review were not widely adopted by IRBs. *Id.* One implementation study of 491 IRBs found that 15% of the protocols reviewed were exempt from the Common Rule. BELL, *supra* note 21, at 9.

<sup>120</sup> Elaine Larson et al., *A Survey of IRB Process in 68 U.S. Hospitals*, 36 J. OF NURSING SCHOLARSHIP 260, 261 (2004).

<sup>121</sup> Trudo Lemmens & Benjamin Freedman, *Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards*, 78 MILBANK Q. 547, 550–55 (2000).

tuted, hope to actually monitor researcher conduct, let alone observe it in vivo, and because it is so often impossible to define “right answers” to ethical dilemmas, OHRP’s oversight uses the proxy of documented procedures. Record-keeping is the classic way that regulated parties prove, and regulating agencies verify, compliance. As long as OHRP’s job is understood to include post-hoc verification of strict regulatory compliance, it will be reviewing records. And as long as the paper record is a significant source of vulnerability to regulatory sanction, institutions will keep those records. With each new problem (whether a real failure of the system or not), more procedures or documents will be added in a one-way paperwork ratchet. At least until some equilibrium is reached, we are likely to see more and more institutional investment in paperwork and documentable compliance procedures. Risk averse institutions will continue to invest more in document production even if OHRP is relatively unintrusive and unaggressive. If we think that the research oversight system is becoming too bureaucratic, the fault is not just in the agency, but in the decision to create the agency—i.e., the insistence that this degree of oversight of institutions is necessary and worth the cost in money, aggravation and effects on useful research.

Institutions also face tool problems. They are expected to review most research, and through that review to detect ethical problems. As the letters show, this is not just a matter of spotting “incorrect” choices about risks and benefits, but actually making sure that the investigator has designed a valid study and included all the relevant facts in the protocol and consent forms. IRBs are held responsible not just for catching errors, but also deliberate non-compliance by researchers.<sup>122</sup> Unfortunately, IRBs—comprised of volunteers who meet periodically to review documents—were not designed to perform these tasks. They started as a kind of enhanced peer review, expected to bring to bear technical expertise and community values but not to act as expert scientific advisory panels—or investigatory bodies.<sup>123</sup> Empirical research strongly indicates that IRBs are poor screens: they are neither highly sensitive—consistently able to detect problems that are present—nor sufficiently specific—consistently able to avoid “finding” problems where none exist.<sup>124</sup> Nor, despite the OHRP’s concern about initial review, and its increasing emphasis on IRB oversight of ongoing research, does a body of volunteer readers seem well-suited to detect protocol omissions or unreported changes by mendacious or over-burdened investigators. For all its criticism of Hopkins’ failure in the death of the healthy volunteer, OHRP never really says (and could not say) that, had the IRB followed procedures,

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<sup>122</sup> Indeed, the Hopkins letter implies that IRBs should routinely conduct independent research to detect risks not known to or disclosed by the researcher in the protocol. See OHRP Letter to Johns Hopkins Univ. (7/19/2001), *supra* note 25, at 5.

<sup>123</sup> Moreno, *supra* note 11, at 10–12.

<sup>124</sup> Studies that submit the same protocols to multiple IRBs consistently find that IRBs find different problems and require different solutions. See sources cited *supra* note 116.

it would have caught the mistakes and omissions. No doubt proper review increases the chances that an IRB member will smell the rat, but one cannot expect the IRB as now constituted to search the literature for drug interactions in every case, or to reliably find deviations from the protocol in ongoing studies. What the IRB can do is make sure required review occurs, and crack down hard on investigators who commit procedural defaults, regardless of whether the defaults actually involve serious risks to subjects or significant deviations from the approved protocol. It is tempting to speculate on the psychological impact on IRB members and institutional risk managers of knowing, at some level, that they face potentially severe sanctions for failing to prevent bad events using a process they know is not up to the job.

For both OHRP and IRBs, the consent form represents the acme of self-defeating ritual compliance. Even the early ethics advocate Henry Beecher knew that informed consent was an imperfect tool,<sup>125</sup> empirical research consistently shows that true informed consent is difficult to achieve and, aside from considerations of readability, probably has rather little to do with the precise wording of a form. Yet IRBs—and, as we show, OHRP—devote enormous attention to specifying the contents and line-editing the text of consent forms.<sup>126</sup> While OHRP oversight is associated with an improvement in consent form readability, IRBs tend to make them harder to understand.<sup>127</sup> This is arguably not just a waste of time, but also a distraction from considering more serious issues, a source of constant annoyance to researchers, and a disservice to the subject.

3. *Over-Deterrence.*—Another explanation for the regulatory paradox may be over-deterrence or “overenforcement.”<sup>128</sup> We found that OHRP was very judicious with its use of the severest sanctions, but the *official* sanctions are not the only sanctions. The Common Rule emerged from a series of scandals, and action in the system has always been responsive to what is reported in the media. Alleged ethical breaches, especially involving subject deaths, are front-page news and increasingly the stuff of civil lawsuits.<sup>129</sup> Researchers and institutions accused of ethical violations face

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<sup>125</sup> Beecher, *supra* note 8, at 1358–60 (noting that informed consent would always be subject to researcher influence and was no substitute for professional ethics).

<sup>126</sup> See sources cited *supra* notes 42, 54.

<sup>127</sup> See, e.g., BELL, *supra* note 21, at 63; Burman et al., *supra* note 116; Adam O. Goldstein et al., *Consent Form Readability in University-Sponsored Research*, 42 J. FAM. PRAC. 606 (1996); Paasche-Orlow et al., *supra* note 54.

<sup>128</sup> See generally Richard Bierschbach & Alex Stein, *Overenforcement*, 93 GEO. L.J. 1743 (2005) (describing the impact of overenforcement of the law).

<sup>129</sup> Cf. Mary R. Anderlik & Nanette Elster, *Lawsuits Against IRBs: Accountability or Incongruity?*, 29 J.L. MED. & ETHICS 220 (2001); Sharona Hoffman & Jessica Wilen Berg, *The Suitability of IRB Liability*, 67 U. PITT. L. REV. 365 (2005); Michelle M. Mello, David M. Studdert & Troyen A. Brennan, *The Rise of Litigation in Human Subjects Research*, 139 ANNALS INTERNAL MED. 40 (2003); Daniel J.

potentially large sanctions imposed by the market in the form of lost opportunities for funding or collaboration, and serious harm to reputation. At least one of the studies investigated in our sample gave rise to a successful tort suit against the institution,<sup>130</sup> and commentators predict that researcher-misconduct and institutional dereliction will be increasingly common targets of civil suits.<sup>131</sup> Researchers have reported the perception that the IRB process at their institutions is run with a cover-your-ass mentality.<sup>132</sup> Finally, cultural factors could be at work: researchers may, as a group, be highly disposed to follow the rules and very unwilling to do anything that might be called unethical.

4. *A Critique from Regulatory Theory.*—Like the Common Law, the Common Rule did not begin with a plan and has never developed one. Yet the system we have today looks like an incompletely theorized and poorly implemented instantiation of the influential regulatory prescriptions associated with the legal scholar Gunther Teubner<sup>133</sup> and, more broadly, many other strains of regulatory scholarship aimed at “proceduralizing” regulation and substituting forms of democratic deliberation for state command and control.<sup>134</sup> Using an IRB to articulate ethical norms for local researchers could be an idea straight from Habermas.<sup>135</sup> Collective deliberation in an environment free of coercion, rather than liberal aggregation of preferences with results enforced by power, produces the rules. Through the IRB,

[e]thical principles can be “known” or rationally decided through social or intersubjective engagements. Instead of asking what an individual moral agent could or would will, without contradiction, to be a universal maxim for all, the

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Powell, *Using the False Claims Act as a Basis for Institutional Review Board Liability*, 69 U. CHI. L. REV. 1399 (2002).

<sup>130</sup> Grimes v. Kennedy Krieger Inst., 782 A.2d 807 (Md. 2001).

<sup>131</sup> See sources cited *supra* note 129.

<sup>132</sup> Burris & Moss, *supra* note 35, at 48; Dawson & Kass, *supra* note 110, at 1214–15.

<sup>133</sup> See Gunther Teubner, *Juridification: Concepts, Aspects, Limits, Solutions*, in JURIDIFICATION OF SOCIAL SPHERES: A COMPARATIVE ANALYSIS IN THE AREAS OF LABOUR, CORPORATE, ANTITRUST AND SOCIAL AND WELFARE LAW 3 (Gunther Teubner ed., 1987) (explaining need for constitutive approaches to regulation); GUNTHER TEUBNER, LAW AS AN AUTOPOIETIC SYSTEM (Anne Bankowska & Ruth Adler, trans., Blackwell 1993) (same).

<sup>134</sup> The details of this literature are beyond the scope of this article, but for excellent overviews see, for example, Julia Black, *Proceduralizing Regulation: Part I*, 20 OXFORD J. LEG. STUD. 597 (2000) [hereinafter Black, *Part I*]; Julia Black, *Proceduralizing Regulation: Part II*, 21 OXFORD J. LEG. STUD. 33 (2001); Michael Moran, *Review Article: Understanding the Regulatory State*, 32 BRIT. J. POL. SCI. 391 (2002).

<sup>135</sup> See, e.g., JURGEN HABERMAS, BETWEEN FACTS AND NORMS: CONTRIBUTIONS TO A DISCOURSE THEORY OF LAW AND DEMOCRACY (William Rehg, trans., MIT Press 1996) (1992); JURGEN HABERMAS, THE THEORY OF COMMUNICATIVE ACTION (Thomas McCarthy, trans., Beacon Press 1984) (1981).

question is what would the members of a real or ideal community agree to as representing their common interests after engaging in deliberation?<sup>136</sup>

An IRB appears to be just the sort of institution a reflexive or responsive regulatory theory would choose. As Teubner sees it from a standpoint in systems theory, traditional, top-down command and control regulation impales the regulator on the horns of a “trilemma”: if the rules are strong enough to change the culture of the regulated organization, they risk crushing the organization’s capacity to maintain robust, independent norms of virtuous behavior; if they are not strong enough, they risk irrelevance; if the rules are “just right,” chances are we are seeing agency capture.<sup>137</sup> Teubner’s solution is to replace external state control with effective internal mechanisms, the “creation of structural conditions for an ‘organizational conscience’” that would balance the demands of the outside world with the conditions of the organization.<sup>138</sup> In the Common Rule, the government has largely delegated the determination of good ethical practice to regulated organizations and required them to internalize the effects they have on others. Rather than “expropriating” social conflicts, OHRP mediates and coordinates conflict between subjects and institutions by demanding institutions respond to complaints and bad outcomes. As in the “responsive regulation” of Ayres and Braithwaite,<sup>139</sup> institutions learn from failure and redirect this learning into their own practices, creating constitutive, reflexive regulatory systems.

Thus one might see the Common Rule as a marvelous instance of cutting edge theory moving into practice, except that in fact the system as we know it today was a product of muddling through and deviates from a regulatory master planner’s template in key ways. First, the IRB is no longer purely or even primarily a body for deliberating about what is ethical. Though it is ill-equipped for the task, the IRB is now also an oversight agency expected to spot bad actors and monitor researcher behavior over time. This aggravates a second problem, which is that the design of the IRB as deliberative body from the start excluded the researcher, who experienced the IRB not as a deliberative body but as a “right answer machine,” a producer of *ex cathedra* judgments on the work of the researcher through a process from which the researcher is typically barred. From the researcher’s point of view, the IRB is not Habermasian deliberation but faceless bureaucracy at its most unchecked. This, in turn, produces a third problem: although the IRB may, in the current system, be required to internalize the costs that questionable research behavior imposes upon subjects,

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<sup>136</sup> Black, *Part I*, *supra* note 134, at 609.

<sup>137</sup> Teubner, *Juridification*, *supra* note 133, at 19–24; see Orly Lobel, *The Renew Deal: The Fall of Regulation and the Rise of Governance in Contemporary Legal Thought*, 89 MINN. L. REV. 342, 283 (2004) [hereinafter Lobel, *The Renew Deal*].

<sup>138</sup> See Black, *Part I*, *supra* note 134, at 603.

<sup>139</sup> See AYRES & BRAITHWAITE, *supra* note 107.

the IRB is not reflexive in relation to the researcher: IRBs typically have no way of knowing, let alone of internalizing, the costs they impose on researchers through their oversight demands. Finally, because OHRP expects the IRB to be an oversight mechanism, and because OHRP is itself under political pressure to monitor institutional compliance, IRBs are in fact subject to considerable top-down control of compliance behavior. Not only is the IRB required to follow detailed procedures and documentation requirements, but even the results of its ethical deliberations can, in instances like the Oregon drug testing study, be overturned by the OHRP.

### C. *A Future: Rebuilding the Governance of Research*

No one denies that there are serious problems in the Common Rule system. Critics have frequently complained of the incongruity of applying ethical principles drawn from medical experimentation to so many different fields of research. In an oft-quoted formulation, a government report concluded that IRBs “review too much, too quickly, with too little expertise.”<sup>140</sup> Much of what they do is described as dispiriting busywork that adds nothing to subject protection.<sup>141</sup> The way IRBs assess risk is said to be faulty, as is their oversight of projects after initial approval.<sup>142</sup> IRBs are subject to too much pressure from their institutions or funders. The regulations IRBs apply are “overly complex, difficult to interpret, . . . at times . . . redundant or inefficient . . . ambiguous and may offer no added protection for subjects.”<sup>143</sup> Research subject and related privacy protections are said to needlessly burden socially valuable research.<sup>144</sup> Critics charge that the system has failed to adapt to changes in the biomedical research field, particularly to the increase in multi-center trials,<sup>145</sup> while others cite problems arising from the extension of Common Rule regulation into fields like public health and qualitative research.<sup>146</sup> Research review is said to have become politi-

<sup>140</sup> OFFICE OF INSPECTOR GEN., *supra* note 7, at 5.

<sup>141</sup> See Robert J. Levine, *Institutional Review Boards: A Crisis in Confidence*, 134 ANNALS INTERNAL MED. 161, 161 (2001).

<sup>142</sup> Coleman, *supra* note 117, at 13–16.

<sup>143</sup> Ralph Snyderman & Edward W. Holmes, *Oversight Mechanisms for Clinical Research*, 287 SCIENCE 595, 597 (2000).

<sup>144</sup> Burman et al., *supra* note 116; Daniel R. Ilgen & Bradford S. Bell, *Conducting Industrial and Organizational Psychological Research: Institutional Review of Research in Work Organizations*, 11 ETHICS & BEHAV. 395 (2001); Douglas B. McCarthy et al., *Medical Records and Privacy: Empirical Effects of Legislation*, 34 HEALTH SERVS. RES. 417 (1999); Karin Nelson et al., *Do Patient Consent Procedures Affect Participation Rates in Health Services Research?*, 40 MED. CARE 283 (2002).

<sup>145</sup> OFFICE OF INSPECTOR GEN., *supra* note 7, at 5–6; Michael C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 NEW ENG. J. MED. 1405 (2002).

<sup>146</sup> PANEL ON IRBS, *supra* note 7; Scott Burris, James Buehler & Zita Lazzarini, *Applying the Common Rule to Public Health Agencies: Questions and Tentative Answers About a Public Health Exemption*, 31 J.L. MED. & ETHICS 638 (2003); Yvonna S. Lincoln & William G. Tierney, *Qualitative Research and Institutional Review Boards*, 10 QUALITATIVE INQUIRY 219 (2004); David Wright, *Creative Nonfiction and the Academy: A Cautionary Tale*, 10 QUALITATIVE INQUIRY 202 (2004); Jack Katz, To

cized, just the continuation of political warfare by other means.<sup>147</sup> The entire enterprise suffers from a focus on the behavior and attitudes of individual researchers rather than the structural social and economic factors that drive researchers to cut corners or worse.<sup>148</sup>

The problems are well-recognized, but for too long, the ends of human subject protection have been used to justify the means. Recommendations for reform have shied away from fundamental change. Certainly there are incremental changes that could make the system work better. OHRP could, for example, develop a materiality standard for review of protocol changes. Were OHRP to develop a model approach to regulating the exemption determination that did not require IRB review, a whole class of minimally risky studies could be taken out of the long review queue.<sup>149</sup> IRBs could, given fewer projects to review, open their deliberations to investigator participation. We suggest, however, that change at the margins may not be enough. A blueprint for a new system is well beyond the scope of this paper, but we offer three broad observations about an approach to more fundamental reforms.

1. *Think in terms of the “governance of research.”*—“Governance” variously defined has emerged as a useful lens for analyzing and reforming regulation of all kinds in a wide variety of fields.<sup>150</sup> The governance ap-

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the Participants in the UCLA, May 2002, Fieldwork Conference (May 8, 2002) (unpublished memorandum on file with author).

<sup>147</sup> See, e.g., Elizabeth Blackburn, *Bioethics and the Political Distortion of Biomedical Science*, 350 NEW ENG. J. MED. 1379 (2004) (describing politicization of president’s bioethics council); Yvonna S. Lincoln & Gaile S. Cannella, *Qualitative Research, Power, and the Radical Right*, 10 QUALITATIVE INQUIRY 175 (2004) (describing politically-motivated attacks on qualitative research).

<sup>148</sup> See, e.g., Marcia Angell, *Is Academic Medicine for Sale?*, 342 NEW ENG. J. MED. 1516 (2000) (discussing the extent academic medicine is linked to pharmaceutical and biotechnology industries and the impact such a relationship has on medical research).

<sup>149</sup> Such a system is being implemented at the University of Chicago: researchers who believe their studies are exempt must file a web-based statement with the IRB office, but can proceed without review of their claim. Personal Communication from Mary Simmerling, Univ. of Chi. (Apr. 7, 2006). OHRP does not require that an IRB review studies to determine whether they are exempt, only that the decision not be left solely to the investigator. OHRP, *Guidance on Written IRB Procedures* (July 11, 2002), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf>.

<sup>150</sup> See, e.g., JOHN BRAITHWAITE, JUDITH HEALY & KATHRYN DWAN, *THE GOVERNANCE OF HEALTH SAFETY AND QUALITY* (2005); John Braithwaite, *Methods of Power for Development: Weapons of the Weak, Weapons of the Strong*, 26 MICH. J. INT’L L. 297 (2004); Scott Burris, Peter Drahos & Clifford Shearing, *Nodal Governance*, 30 AUSTL. J. LEGAL PHIL. 30 (2005); Lobel, *The Renew Deal*, *supra* note 137; Orly Lobel, *Interlocking Regulatory and Industrial Relations: The Governance of Workplace Safety*, 57 ADMIN. L. REV. 1071 (2005); Louise G. Trubek, *New Governance Practices in U.S. Health Care* (Univ. of Wis. Legal Studies Research Paper No. 1006, 2005), available at <http://ssrn.com/abstract=861206>; Louise G. Trubek, *New Governance and Soft Law in Health Care Reform* (Univ. of Wis. Legal Studies Research Paper No. 1018, 2006), available at <http://ssrn.com/abstract=908674>; David M. Trubek & Louise G. Trubek, *New Governance and Legal Regulation: Complementarity, Rivalry or Transformation* (Univ. of Wis. Legal Studies Research Paper No. 1022, 2006), available at <http://ssrn.com/abstract=908229>. For a review, see Michael Kempa, Clifford Shearing & Scott

proach is characterized by recognition of the plurality of governors and governance tools present in social systems. It is not just about government-enforced rules, but rather embraces the many non-state and hybrid institutions that can and do govern behavior. The Common Rule system does have innovative design elements, albeit poorly theorized and badly implemented ones. There is a foundation to build on.

The lens of governance is also useful because it allows reformers to grasp that in practice we are dealing with a system for regulating research, not just protecting human subjects. Seeing the system this way puts the need for trade-offs and hard choices squarely on the table. “Ethical inflation”—the identification of ever subtler forms of unethical behavior and subject harm—may be a marker of human moral improvement but when imposed on researchers and society by IRBs and professional ethicists can feel an awful lot like moral imperialism. The pious intonation of the mantras that human subject protection is the prime concern, and that there is no tension between promoting research and protecting subjects, is tiresome and unilluminating of the hard choices research ethics can pose. As currently governed, the research world seems to lack both the concept of marginal cost and space for deliberating the real value of the next increment of regulatory expansion.

2. *Base reform on a nuanced empirical account of the practice of research, the risks to subjects, and the implementation of the Common Rule.*—The trickle of empirical work on the implementation of the Common Rule has finally, in recent years, grown into a moderately healthy brook. That is good, but we still do not know enough about basic questions like how much harm to subjects occurs, whether or how much prior review or other required procedures reduce risks, how risks and regulatory efficacy vary across different fields of research, how the operation of the system influences researcher attitudes and behavior, how structural factors drive researcher or IRB behavior, or how much the whole system costs. The research cited throughout this paper is more than enough to suggest that the answers are not easy and that there is every reason to believe the current system is working on flawed assumptions and using ineffective tools.

3. *Face up to the dysfunctional environment.*—The governance of research unfolds in a political and economic environment that is not conducive to good practice. On the political side, Phillip Pettit has eloquently described the emergence of human subject protection as a process of cyclical response to scandal.<sup>151</sup> It is almost possible to describe the current sys-

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Burris, *Changes in Governance: A Background Review* (2005), available at [http://www.temple.edu/lawschool/phrhcs/salzburg/Global\\_Health\\_Governance\\_Review.pdf](http://www.temple.edu/lawschool/phrhcs/salzburg/Global_Health_Governance_Review.pdf).

<sup>151</sup> PHILIP PETTIT, *Instituting a Research Ethic: Chilling and Cautionary Tales*, in RULES, REASONS, AND NORMS 378 (2002).

tem as a monument to unintended consequences, except that there have always been elites whose self-interest was served by raising the cry of research abuse. The denunciations of research abuse of human subjects that emerged in the late 1950s and early '60s were courageous; the medical research community was in active denial about its misbehavior and the public was in the dark. Official action was more than understandable in the face of scandals like thalidomide and Tuskegee. But what was creative norm-entrepreneurship and political leadership in one time seems now to have devolved in many instances into "gotcha" politics and self-serving self-righteousness. The culture of research has radically changed since the post-war generation of the 1950s flattered itself that participation in research was a duty and a privilege, and it is facetious to think otherwise. Uncritical conflation of "intangible harms" or social risks with the sort of mortal dangers the early whistle-blowers documented sheds heat but little light on how to deal with present-day challenges. Even a regulatory system as big as the Common Rule's cannot catch all problems; there will be a rate of error and problems. Our society must accept that bad results are not always a scandal and that "more" oversight is not always the answer.

Governance reform must also address the biomedical industrial complex and its role in ethical inflation and the expansion of the infrastructure. The bioethics profession is part of the complex, increasing its own capital by broadening the prevailing definitions of harm and unethical conduct.<sup>152</sup> There is a great deal of reasonable concern about how pharmaceuticals are developed in this country, but to deal with this problem through oversight of researchers is to wag the dog by the tail. The seminal article in the research ethics movement, Beecher's 1964 catalogue of abusive studies, was both prophetic and pathetic in its handling of the structural determinants of misconduct: The author begins the paper with a powerful description of the expanding biomedical research industry and the pressures put on young researchers by money and ambition to advance in their university careers. In the end, however, the only solutions he offers are greater attention to informed consent and researcher virtue. It is essential to agree once and for all that the problem of subject abuse is not just a matter of bad researchers or improperly drafted consent forms. Researchers and institutions are themselves caught up in powerful currents of economic and social pressure.<sup>153</sup> The governance of research must look outward at the expanding

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<sup>152</sup> As David Hyman notes in this volume, "IRB approval provides no protection against criticism by novice bioethicists looking to 'make their bones' on the latest controversy, or established bioethicists who want to see their names in print." David Hyman, *IRBs: Is this the Least Worst We Can Do?*, 101 NW. U. L. REV. 749, 771–72 (2007).

<sup>153</sup> See, e.g., Raymond De Vries, Melissa S. Anderson & Brian C. Martinson, *Normal Misbehavior: Scientists Talk About the Ethics of Research*, 1 J. EMPIRICAL RES. ON HUMAN RES. ETHICS 43 (2006); Gatter, *supra* note 113; David Healy, *Conflicting Interests in Toronto: Anatomy of a Controversy at the Interface of Academia and Industry*, 45 PERSP. BIOLOGY & MED. 250 (2002); Brian C. Martinson et al., *Scientists' Perceptions of Organizational Justice and Self-Reported Misbehaviors*, 1 J. EMPIRICAL RES.

circles of influence around the researcher, from standards for promotion and tenure through the relations of those who fund research and institutions to the ways we now organize the process of testing new drugs and devices.

We do not pretend that more favorable conditions of possibility are likely to emerge, but there is no point in pretending that reform is simply a matter of good information and creative regulatory technique. If research matters to the country, and real protection of human subjects is a priority, then political leaders, media, and other opinion shapers and policy makers have to take responsibility for engendering an environment conducive to real reform.<sup>154</sup>

#### CONCLUSION

Ethics as a practice of systematic inquiry can illuminate and enrich health practice and research. Ethics as a set of regulatory requirements, and more broadly as a compulsory and accusatory way of conceptualizing research and practice issues, can have a countervailing negative effect. As applied under the Common Rule, ethical considerations are rapidly reaching the point of parody in some realms, displaying a punctilious and myopic stringency even as, paradoxically, the pressures on researchers to disregard subject welfare are as great as ever. The IRB system is entering a phase of regulatory sclerosis: A combination of poor design, unrealistic expectations, and a one way ratchet of enforcement is leading to a steady increase in the responsibilities (and the paperwork) of IRBs and the intrusiveness of the review process, while other regulatory systems (like tort and federal fraud regimes) wait their turn in the wings. The time has come for those who support ethical research to save the current system from its own dominance.

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ON HUMAN RES. ETHICS 51 (2006); P. Sleight, *Where Are Clinical Trials Going? Society and Clinical Trials*, 255 J. INTERNAL MED. 151 (2004).

<sup>154</sup> This study and its findings are subject to several limitations to the study. First, the OHRP redacts any unresolved concerns from its letter, so the study may underestimate the number and perhaps the severity of problems identified. In some investigations, the letters posted left some issues unresolved, so the remedy data is also incomplete. This study relied on the OHRP's side of the story, including its summary of the institutions' responses to those letters. As a result, it was difficult to ascertain exactly how serious these allegations were in many cases. More broadly, the assessment of OHRP as a "responsive" regulator carefully calibrating its investigations and sanctions is taken from the letters and from an interview with the agency's director. Regulated institutions may see things differently.

