

RESEARCH ETHICS COMMITTEES (RECS)/INSTITUTIONAL REVIEW BOARDS (IRBS) AND THE GLOBALIZATION OF CLINICAL RESEARCH: CAN ETHICAL OVERSIGHT OF HUMAN SUBJECTS RESEARCH BE STANDARDIZED?

INTRODUCTION

Current United States' policy requires federally funded research studies involving human subjects to be approved by an interdisciplinary committee called an institutional review board (IRB).¹ IRBs exist to protect the safety and welfare of human subjects participating in research studies. Although oversight of human subjects research and, consequently, IRBs, is governed by federal regulations, the operation of IRBs remain largely mysterious to those other than IRB members themselves. This Note reviews the establishment of both United States regulations and international guidelines governing human subjects research, the changing environment of biomedical research, and potential reforms for improving the efficiency and efficacy of ethical review performed by IRBs.

Part I of this Note reviews the establishment of the federal regulations governing human subjects research that originates in the United States as well as the ethical principles that guided their creation. Part II presents current policies governing the structure and function of IRBs and also describes potential policy revisions relevant to the function of IRBs. Part III examines current controversies regarding research oversight systems. Finally, Part IV offers recommendations for improving human research subject oversight.

1. Committees that review the ethics of human subjects research are called IRBs in the United States. Different names are used for such committees in other countries, including research ethics committees or ethics review committees. Sandra L. Alfano, *Conducting Research with Human Subjects in International Settings: Ethical Considerations*, 86 *YALE J. BIO. & MED.* 315, 317 (2013). In this Note, references to committees that oversee human subjects in the United States will be identified as IRBs. References to such committees in nations outside the United States will be identified as Research Ethics Committees (RECs).

I. BACKGROUND

A. *Regulating Human Subjects Research*

The establishment of ethical standards for research involving human subjects on an international scale almost certainly began with the Nuremberg Code in 1947.² Subsequently, in 1964, the World Medical Association (WMA) adopted a statement of ethical principles for conducting medical research with humans, known as The Declaration of Helsinki.³ Similarly, the Council for International Organizations of Medical Sciences (CIOMS)⁴ has published ethical guidelines for research involving human subjects that emphasize ethical review and informed consent.⁵

Before the 1960s, the ethics of research involving human subjects in the United States was a matter for individual research investigators to address. By the mid-1960s, however, the National Institutes of Health

2. Ruth Macklin, *Appropriate Ethical Standards*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 711, 711 (Ezekiel J. Emanuel et al. eds., 2008). The Nuremberg Code, delivered in August 1947 as the final judgment in the Doctors Trial at Nuremberg, Germany, consists of ten rules directed at protecting human research subjects. George J. Annas & Michael A. Grodin, *The Nuremberg Code*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 136, 138 (Ezekiel J. Emanuel et al. eds., 2008). During the trial, United States judges heard evidence of murder and torture supervised by Nazi physicians in the name of medical research. *Id.* at 136. A central strength of the Code is its reliance on the principle of informed consent “insisting that the voluntary, competent, informed, and understanding consent of the research subject is a necessary (but not sufficient) prerequisite for lawful human experimentation . . .” *Id.* at 138.

3. The WMA was founded in Paris in 1947 as an association for national medical associations. *History*, WORLD MEDICAL ASSOCIATION, Nov. 8, 2015, <http://www.wma.net/en/60about/70history/index.html>. At the time it was established, members were particularly concerned with the violations of human rights and ethics that had taken place in Germany and elsewhere during World War II. *Id.* The Declaration of Helsinki was adopted by the WMA at its annual General Assembly in Helsinki in 1964. Richard E. Ashcroft, *The Declaration of Helsinki*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 141, 141–43 (Ezekiel J. Emanuel et al. eds., 2008). The Declaration of Helsinki asserts: “Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.” *WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects*, WORLD MEDICAL ASSOCIATION, <http://www.wma.net/en/30publications/10policies/b3/index.html> (last visited Oct. 23, 2015). The Declaration emphasizes that some research populations include individuals who cannot give or refuse consent and those who may be unduly influenced. Such groups should thus “receive specifically considered protection.” *Id.*

4. CIOMS is a collaborative entity of two United Nations agencies—the World Health Organization (WHO) and the United Nations Educational, Scientific, and Cultural Organization (UNESCO). Juhana E. Idänpään-Heikkilä & Sev S. Fluss, *International Ethical Guidance From the Council for International Organizations of Medical Sciences*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 168, 168 (Ezekiel J. Emanuel et al. eds., 2008).

5. See *CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects*, COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES, http://www.cioms.ch/images/stories/CIOMS/guidelines/guidelines_nov_2002_blurb.htm (last visited Oct. 23, 2015).

(NIH), an agency of the Department of Health and Human Services (DHHS),⁶ was devoting more resources to clinical research activities and establishing itself as the primary funding vehicle for biomedical research.⁷ As government funding for biomedical research increased, officials became concerned about the potential conflict of protecting subjects from harm while encouraging researchers to pursue studies to develop new knowledge.⁸ In addition, the public remained disturbed about the horrific abuses suffered by prisoners in the name of experimentation during World War II.⁹ Responding to this climate, the NIH Director proposed in 1965 that the agency establish a requirement for investigators to submit research protocols for peer evaluation of risks the proposed studies presented to human subjects.¹⁰ In 1966, agency authorities agreed to a new rule requiring that institutions receiving federal funding for research involving human subjects establish committees to consider the ethics of proposed research studies involving human subjects.¹¹ The committee would “assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to determine informed consent, and (3) of the risks and potential medical benefits of the investigation.”¹² Adoption of the new rule thus produced the first IRBs.

In 1972, the need for additional regulatory action addressing ethics review was reinforced by revelations of a United States research scandal: The nation learned about the Tuskegee Syphilis Study—a government-sponsored study in which nearly four hundred African American men had been deprived of treatment for syphilis for more than thirty years.¹³ The study, started in the 1930s, continued long after the discovery of penicillin and after the review and approval by an IRB at the Tuskegee Institute.¹⁴ In 1974, Congress responded by passing legislation creating the National

6. Until 1980, DHHS was the Department of Health, Education, and Welfare (DHEW). *Historical Highlights*, U.S. DEP’T OF HEALTH & HUMAN SERVICES, Nov. 8, 2015, <http://www.hhs.gov/about/historical-highlights/index.html>.

7. Charles R. McCarthy, *The Origins and Policies That Govern Institutional Review Boards*, in *THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS* 541, 543 (Ezekiel J. Emanuel et al. eds., 2008).

8. *Id.*

9. *Introduction*, in *THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS* 3, 3–4 (Ezekiel J. Emanuel et al. eds., 2008).

10. McCarthy, *supra* note 7, at 542.

11. *Id.* at 546.

12. *Id.*

13. James H. Jones, *The Tuskegee Syphilis Experiment*, in *THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS* 86, 86 (Ezekiel J. Emanuel et al. eds., 2008).

14. McCarthy, *supra* note 7, at 547.

Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (“National Commission”).¹⁵ Four years later, the National Commission issued a report outlining recommendations for regulations governing IRBs based in part on review of how IRBs performed during their first decade. The National Commission presented its belief that human subjects should be protected by *local* review committees governed by uniform *federal* regulations. The National Commission further recognized the importance of placing review at the local level with individuals who could best understand the research environment.¹⁶ At the same time, however, incidents such as The Tuskegee Syphilis Study made it clear that uniform, national oversight for IRBs was necessary.¹⁷

The National Commission recommended that a single federal office be established to provide accreditation and compliance assessment of IRBs as well as ethical education activities for IRB members.¹⁸ In addition, the Commission recommended that IRBs: be made up of individuals from “diverse backgrounds,” include one member not affiliated with the institution, maintain sufficient records, and have the authority to approve, require modifications of, and disapprove all research proposals involving human subjects at the institution.¹⁹ The Commission further recommended that federal regulations be adopted that would require IRBs: to assess the risks and benefits of research to potential human subjects, ensure that the process of selecting human subjects was equitable, and ensure informed consent was obtained and appropriately documented for all research studies.²⁰

In 1978, the National Commission published a document commonly referred to as The Belmont Report,²¹ which identified three moral

15. *See id.* at 548 (referring to National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974)).

16. U.S. DEPT. OF HEALTH, EDUC. & WELFARE, DHEW Pub. No. (OS) 78-0008, NAT’L COMM’N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, REPORT AND RECOMMENDATIONS INSTITUTIONAL REVIEW BOARDS I (1978).

17. The Commission emphasized the critical need for independent ethical review in general: [I]nvestigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others, who are independent of the research, must share the responsibility, because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research. *Id.*

18. *Id.* at 10.

19. *Id.* at 13.

20. *Id.* at 19–21.

21. The Belmont Report is a document outlining important moral principles that was written and published by the National Commission for the Protection of Human Subjects of Biomedical Research in 1978. Tom L. Beauchamp, *The Belmont Report*, in THE OXFORD TEXTBOOK OF CLINICAL

principles that should guide the conduct of ethical research: respect for persons, beneficence, and justice.²² The Belmont principles provided a guide for IRBs and a framework for drafting federal regulations.²³ In 1981, the Department of Health and Human Services (DHHS)—then the Department of Health, Education and Welfare—adopted regulations designed to protect human subjects that incorporated many of the recommendations of the National Commission.²⁴ Ten years later, fourteen other federal departments and agencies joined DHHS in adopting a uniform set of rules for the protection of human subjects. These rules closely resembled the earlier regulations and later became known as the Common Rule.²⁵

The regulations of the Common Rule require that researchers who are subject to them provide written assurance that they are meeting the requirements of the Common Rule. Aside from the assurance process and its requirements for reporting violations, “there is no other formal mechanism whereby the activities of IRBs are . . . monitored by the federal government.”²⁶ Despite the lack of close government oversight, there has been considerable success in minimizing human subjects abuse since the development of regulations governing IRBs. In fact, following a comprehensive review of the regulations as well as data on research outcomes, the Presidential Commission for the Study of Bioethical Issues recently concluded that “the current U.S. system provides substantial protections for the health, rights, and welfare of research subjects and, in general, serves to ‘protect people from harm or unethical treatment’ when they volunteer to participate as subjects in scientific studies supported by

RESEARCH ETHICS 149, 149 (Ezekiel J. Emanuel et al. eds., 2008). It is frequently used in the United States as well as other countries to frame discussions about ethical considerations in medical research. *Id.*

22. *The Belmont Report*, U.S. DEP’T OF HEALTH & HUMAN SERVICES, Apr. 18, 1979, <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. In providing a historical account of the development of The Belmont Report, Tom Beauchamp writes: “The key organizing conception underlying the Commission’s presentation of [the] principles and their use was the following: Respect for persons applies to informed consent; beneficence applies to risk-benefit assessment; and justice applies to the selection of research participants.” Beauchamp, *supra* note 21, at 150.

23. *Id.*

24. Joan P. Porter & Greg Koski, *Regulations for the Protection of Humans in Research in the United States: The Common Rule*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 156, 156–57 (Ezekiel J. Emanuel et al. eds., 2008) (referring to regulations later incorporated into 45 C.F.R. pt. 46).

25. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (proposed July 26, 2011) (to be codified at 45 C.F.R. pt. 46, 160, 164) [hereinafter ANPRM].

26. Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 99–100 (1993).

the federal government.”²⁷ However, a growing number of researchers have criticized the IRB process for creating bureaucratic impediments to research while providing minimal, if any, ethical protections for human subjects.²⁸

B. Globalization of Clinical Research

The Common Rule remains significantly unchanged since it took effect in 1991.²⁹ In contrast, the world of biomedical research looks vastly different. Funding for federally supported medical research alone nearly doubled between 1986 and 1995.³⁰ Perhaps most significantly, there has been a dramatic increase in the number of research studies performed at multiple sites as well as a significant global expansion of biomedical research.³¹ For example, the number of publications reporting on multicenter studies has increased more than three fold between 1990 and 1999.³² Similarly, the number of countries serving as clinical sites for research supported by United States institutions more than doubled

27. *Moral Science: Protecting Participants in Human Subjects Research*, PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES 1, 42 (Dec. 2011), available at <http://bioethics.gov/sites/default/files/Moral%20Science%20June%202012.pdf> [hereinafter *Moral Science* 2011].

28. Simon N. Whitney & Carl E. Schneider, *Viewpoint: A Method to Estimate the Cost in Lives of Ethics Board Review of Biomedical Research*, 269 J. INTERNAL MED. 396, 400–01 (2011). See generally, George Silberman & Katherine L. Kahn, *Burdens on Research Imposed by Institutional Review Boards: The State of the Evidence and Its Implications for Regulatory Reform*, 89 MILBANK Q. 599 (2011); Infectious Diseases Society of America, *Grinding to a Halt: The Effects of the Increasing Regulatory Burden on Research and Quality Improvement Efforts*, 49 CLINICAL INFECTIOUS DISEASES 328 (2009).

29. ANPRM, *supra* note 25. See also Porter & Koski, *supra* note 24, at 165–66.

30. “In the past two decades, phenomenal growth has occurred in federally and industry-sponsored biomedical research. Federal expenditures for medical and health research conducted in the United States and in foreign countries almost doubled from \$6.9 billion to \$13.4 billion between 1986 and 1995.” *Ethical and Policy Issues in Research Involving Human Participants*, NAT’L BIOETHICS ADVISORY COUNCIL 4 (Aug. 2001), available at <https://bioethicsarchive.georgetown.edu/nbac/human/overvol1.pdf> [hereinafter NBAC 2001].

31. See, e.g., Ezekiel J. Emanuel and Jerry Menikoff, *Reforming the Regulations Governing Research with Human Subjects*, 365 NEW ENG. J. MED. 1145 (2011); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 J. AM. MED. ASS’N 360 (2003); Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816 (2009); *Institutional Review Boards: A Time for Reform*, DEP’T OF HEALTH AND HUMAN SERV. 12–13 (June 1998), available at www.oig.hhs.gov/oei/reports/oei-01-97-00193.pdf [hereinafter *Time for Reform*].

32. McWilliams et al., *supra* note 31, at 362. The authors evaluated results from PubMed to identify the number of published multicenter epidemiology studies from 1974 to 2002. The authors found that “the number of epidemiology and genetic epidemiology multicenter studies increased 4- to 5-fold every 5 years during [the period from 1985 to 1999].” *Id.*

between 1995 and 2005.³³ Furthermore, although a great deal of research continues to occur in academic medical centers, studies are now also performed outside of academic settings, such as in industry-operated centers, community hospitals, and private physicians' offices.³⁴ IRB activity, however, remains largely with academic boards that may have little to no experience with non-traditional research environments nor an understanding of cultural norms outside of the United States.

II. CURRENT POLICY AND POTENTIAL REVISIONS

Current policy governing IRBs and oversight of research involving human subjects is codified in the regulations of the Common Rule. Part A of this section explains the Common Rule and Part B identifies suggested revisions to the regulations.

A. *The Common Rule*

The Common Rule applies to research involving human subjects that is conducted, supported, or otherwise subject to regulation by any of the federal departments or agencies that have adopted the Rule. Many Common Rule provisions directly address the structure and function of IRBs. For example, under the regulations an IRB must have at least five members including at least one scientist, one non-scientist, and one individual who is not affiliated with the institution.³⁵ Furthermore, in order to approve a study, an IRB must determine that: (1) risks to subjects are minimized; (2) the balance between risks to subjects and the anticipated benefits are reasonable; (3) selection of research subjects is equitable and the needs of vulnerable populations have been considered; (4) subjects will receive information that allows them to make an informed choice about participation; (5) subjects' informed consent will be properly documented; (6) adequate data monitoring is in place; and (7) the privacy and confidentiality of research subjects and their health data will be

33. Glickman et al., *supra* note 31. Glickman notes that the large populations and lower costs of research in countries such as China and India allow researchers to expedite studies that are expanded to those regions. In addition, Glickman emphasized that "testing in developing countries is also attractive to pharmaceutical and device companies because it can help them overcome regulatory barriers for drug approval in these countries in which the population size alone offers the promise of expanding markets." *Id.* at 817.

34. Time for Reform, *supra* note 31, at 4; Carl H. Coleman, *Foreward*, 32 SETON HALL L. REV. 489, 489 (2002).

35. 45 C.F.R. § 46.107, *infra* note 94.

maintained.³⁶ The Common Rule also provides for an expedited review process for research in certain categories³⁷ that involves no more than minimal risk.³⁸ Studies qualifying for expedited review may be reviewed and approved by a single member of the IRB—often the chairperson—rather than the full board.³⁹

36. 45 C.F.R. § 46.111. In full, the regulation provides the criteria for IRB approval of research as follows:

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Id.

37. *Protection of Human Subjects: Categories of Research That May Be Reviewed by the IRB through an Expedited Review Procedure*, 63 FED. REG. 60,364–67 (1998) [hereinafter *Expedited Categories*].

38. “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” 45 C.F.R. § 46.102.

39. 45 C.F.R. § 46.110.

(a) The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments

Although the regulations that make up the Common Rule have remained largely unchanged for decades, and have been successful in promoting ethical human research, criticism of the regulations abound.⁴⁰ In response to these criticisms, as well as suggested reforms by the National Bioethics Advisory Commission and the Institute of Medicine, DHHS convened a working group to consider revisions to the Common Rule.⁴¹ DHHS published the group's work in the Federal Register in July 2011 as an Advanced Notice of Proposed Rulemaking (ANPRM).

B. Advanced Notice of Proposed Rulemaking (ANPRM)

The ANPRM identified seven areas for potential reform and solicited public comment on whether and how the Rule should be changed.⁴² The

and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office of Human Research Protections, HHS, or any successor office.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under the expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

Id.

40. Critics cite unjustified costs and burdens associated with redundant review of multicenter research studies by multiple IRBs, IRB review of research activities that are outside of the scope of biomedical research, and IRBs' increased focus on improving readability of informed consent documentation while only making forms longer and less intelligible. Steven Joffe, *Revolution or Reform in Human Subjects Research Oversight*, 40 J.L. MED. & ETHICS 922, 923 (2012); Scott Kim, Peter Ubel, & Raymond DeVries, *Pruning the Regulatory Tree*, 457 NATURE 534, 534–35 (2009); Norman Fost & Robert J. Levine, *The Dysregulation of Human Subjects Research*, 298 NATURE 2196, 2196–97 (2007); see generally *The Illinois White Paper: Improving the System for Protecting Human Subjects: Counteracting IRB "Mission Creep"*, CENTER FOR ADV. STUD. (2005), available at http://papers.ssm.com/sol3/papers.cfm?abstract_id=902995 (last visited Sept. 17, 2015); Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANNALS OF INTERNAL MED. 282 (2004).

41. ANPRM, *supra* note 25, at 44512–13; NBAC 2001, *supra* note 22; RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS (Daniel D. Federman et al. eds., 2002) [hereinafter IOM 2002].

42. ANPRM, *supra* note 25. The ANPRM considered the following seven changes to the regulatory framework:

ANPRM identified four areas for reform with particular relevance to IRBs: (1) a need to better calibrate the degree of research oversight to the degree of risk posed by the research; (2) a need to eliminate redundancy of IRB review in multicenter domestic studies; (3) a need to improve the process of obtaining informed consent; and (4) a need to expand federal oversight of human subjects research to privately funded studies.⁴³ The ANPRM will be followed by a notice of proposed rulemaking to identify the proposed regulations and another period for public consideration and comment before any changes are made.

1. Ensuring Risk-Based Protections

The current regulations divide human research studies into one of three oversight categories: exempt, expedited review, or convened IRB review.⁴⁴ Studies exempt from review include those involving the use of educational tests or existing data so long as a subject's identifiable information is not linked to data.⁴⁵ Studies that fall into one of several categories⁴⁶ and

(1) Refinement of the existing risk-based regulatory framework; (2) Utilization of a single IRB review of record for domestic sites of multi-site studies; (3) Improvement of consent forms and the consent process; (4) Establishment of mandatory data security and information protection standards for all studies that involve identifiable or potentially identifiable data; (5) Establishment of an improved, more systematic approach for the collection and analysis of data on unanticipated problems and adverse events; (6) Extension of federal regulatory protections to all research, regardless of funding source, conducted at institutions in the U.S. that receive some federal funding from a Common Rule agency for research with human subjects; and (7) Improvement in the harmonization of regulations and related agency guidance.

Id. at 44514.

43. ANPRM, *supra* note 25, at 44514.

44. *Id.*

45. 45 C.F.R. § 46.101(b). The regulation stipulates that:

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' response outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that

involve no more than minimal risk to the human subject⁴⁷ may qualify for expedited review.⁴⁸ A study that qualifies for expedited review can be reviewed by a single designated IRB member who acts in place of the board.⁴⁹

Currently, the majority of research studies involving human subjects must undergo review by a convened IRB. To be approved, a study must

is not exempt under [(2)] of this section, if:(i) The human subjects are elected or appointed public officials or candidates for public office; or ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Id.

46. There are currently nine categories of research that are eligible for expedited review. They include, for example, research that involves collecting small amounts of blood from healthy, non-pregnant adults and research that utilizes certain noninvasive clinical procedures such as magnetic resonance imaging. For complete list, *see* Expedited Categories, *supra* note 37.

47. *See supra* note 38 for the Common Rule definition of minimal risk.

48. 45 CFR § 46.110; Expedited Categories, *supra* note 37. The Common Rule specifies:

An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list [of categories of research that may be eligible for expedited review] and found by the reviewer(s) to involve no more than minimal risk, (2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 46.108(b).

Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

45 CFR § 46.110(b),(c).

49. The designated member who reviews research proposals qualifying for expedited review may be the chairperson or another experienced reviewer who is on the IRB. 45 CFR § 46.110(b).

receive the votes of a majority of the board.⁵⁰ The ANPRM contemplates maintaining the requirement of review by a convened IRB for research involving more than minimal risk.⁵¹ But the ANPRM contemplates expanding the number of research projects that qualify for expedited review.⁵² Furthermore, the ANPRM considers reducing the paperwork required for expedited review.⁵³ Officials could also provide templates of protocols and consent documents for common types of studies that researchers could adapt.⁵⁴ Finally, the ANPRM contemplates expanding the category of research activities that qualify as exempt (referred to as “excused” in the ANPRM).⁵⁵

2. Streamlining IRB Review of Multicenter Studies

Under current regulations, the IRBs in each institution participating in a multicenter study must approve the study.⁵⁶ Multiple institutions participating in the same study frequently have their own IRBs review the study protocol and consent documents.⁵⁷ To avoid duplicative efforts that do not contribute additional safeguards to human subjects, the ANPRM contemplates a change in the Common Rule that would require institutions participating in multicenter studies to select a single IRB as the IRB of record.⁵⁸ The proposed change would apply to studies conducted exclusively in the United States that do not require FDA approval.⁵⁹

50. According to the Common Rule, IRBs must “review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.” 45 CFR § 46.108(b).

51. No continuing annual review would be required if the ongoing research was limited to review of existing data. ANPRM, *supra* note 25, at 44516.

52. To accomplish this goal, federal officials would routinely reassess and update the list of research activities that qualify for expedited review. They would also revise the regulations to include a presumption that research studies involving activities on the list present minimal risk and thus qualify for expedited review. *Id.*

53. *Id.* at 44517.

54. *Id.*

55. *Id.* at 44518. The exempt category would be expanded by exempting research on biospecimens or existing data even if the data or specimens are linked to identifying information. *Id.* at 44, 519.

56. However, studies may be reviewed jointly for two institutions by one IRB. 45 CFR § 46.114.

57. ANPRM, *supra* note 25, at 44521–22; Joffe, *supra* note 40, at 923.

58. ANPRM, *supra* note 25, at 44522.

59. The ANPRM notes that the change is being considered only for domestic sites in multicenter studies as “independent local IRB reviews of international sites are appropriate because it might be difficult for an IRB in the U.S. to adequately evaluate local conditions in a foreign country that would play an important role in the ethical evaluation of the study.” *Id.* at 44521–22.

3. *Improving Informed Consent*

Currently, under the Common Rule, researchers must obtain and document that they have obtained informed consent from a subject before research involving that subject can commence.⁶⁰ Furthermore, the consent process and associated forms used by researchers must be reviewed and approved by an IRB. Although only minor changes have been made to the regulations concerning informed consent in the past forty years, commentators have noted that during that same period the informed consent forms presented to potential subjects have gotten longer and IRBs have spent considerably more time reviewing them without improving the ability to obtain actual informed consent.⁶¹ The ANPRM acknowledges

60. 45 CFR § 46.116. The regulations currently require that the documents used to obtain a subject's consent include the following information:

- (1) A statement that the study involves research, an explanation of the purposes of the research and expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- (8) A statement 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.

Id.

61. See generally Ilene Albala, Margaret Doyle, & Paul S. Appelbaum, *The Evolution of Consent forms for Research: A Quarter Century of Changes*, 32 IRB: ETHICS & HUM. RESEARCH 7 (2010); William Burman et al., *The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium*, 24 CONTROLLED CLIN. TRIALS 245 (2003); Jerry Menikoff & Edward P. Richards, *What the Doctor Didn't Say: The Hidden Truth about Medical Research* 113–23 (2006); Carl E. Schneider, *The Hydra*, 40 HASTINGS CTR. REP. 9 (2010). Results of a study performed by William Burman and colleagues illustrates the problem. Burman's study evaluated the review process of two protocols from a multicenter study that was reviewed separately by twenty-five different local IRBs. The study found that IRB "review was a time-consuming process, requiring a median of 30 hours of work by the local study site and more than 3 months of calendar time to complete." William Burman, et al. *supra* at 251. Although the IRBs did not require changes in the protocols, they did require a median of 46.5 changes in each consent form. *Id.* at 245. The authors concluded that only 1.5% of those changes "were thought to represent a need to fit specific local

that the current “[l]ength and high reading levels [of informed consent forms] may inhibit people from reading the full document and understanding relevant information.”⁶² As a result, the ANPRM contemplates changes to the regulations that would specifically identify content to be included in the consent forms—in part through making template consent forms available to researchers—and also limit the length of certain sections of the documents.⁶³ In addition, the ANPRM contemplates changes to the Common Rule that would expand the conditions under which the requirements for informed consent could be waived.⁶⁴ In particular, the ANPRM notes that criteria for obtaining a waiver under the present regulations may not permit researchers to obtain waivers under circumstances where they are seeking to conduct research on persons whose culture or customs disfavor having individuals sign

conditions.” *Id.* at 249. Furthermore, although the majority of the changes did not alter the substance of the consent forms they did effect their quality. Following the changes the forms were longer, sentences were wordier and the authors found that the overall reading level was higher than before the changes. They reported that after the IRB-required changes 41% of the forms “had an inappropriately high reading grade level.” *Id.*

62. ANPRM, *supra* note 25, at 44522.

63. *Id.* at 44523.

We are considering a number of modifications to the regulations to improve consent forms, including (1) prescribing appropriate content that must be included in consent forms, with greater specificity than is provided in the current regulations; (2) restricting content that would be *inappropriate* to include in consent forms; (3) limiting the acceptable length of various sections of a consent form; (4) prescribing how information should be presented in consent forms, such as information that should be included at the very beginning of the consent form, or types of information that should be included in appendices and not in the main body of the consent form; (5) reducing institutional “boilerplate” in consent forms (that is, standard language that does little to genuinely inform subjects, and often is intended to primarily protect institutions from lawsuits); and (6) making available standardized consent form templates, the use of which could satisfy applicable regulatory provisions.

Id.

64. Currently, an IRB may waive the requirement to obtain informed consent if the IRB determines that the research will be conducted by or subject to government approval; is designed to “study, evaluate, or otherwise examine . . . public benefit of service programs,” or procedures, services or possible changes to such programs; AND “[t]he research could not practically be carried out without the waiver . . .” 45 CFR § 46.116(c). Waiver of informed consent is more commonly obtained by satisfying the requirements of 45 CFR § 46.116(d):

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents 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.

Id.

documents.⁶⁵ To address this concern the ANPRM requests comments and suggestions regarding “. . . circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent.”⁶⁶

4. *Expanding Federal Regulations*

At present, the federal regulations governing the review of human subjects research apply only to research that is supported or conducted by a federal department or agency that has adopted them.⁶⁷ However, the Food and Drug Administration (FDA) also applies much of the Common Rule to privately funded research on drugs and devices seeking FDA approval.⁶⁸ As the ANPRM notes, most institutions voluntarily require IRB approval for research that is not supported by federal funds, but such approval is not currently a federal requirement.⁶⁹ The ANPRM contemplates a new regulation requiring IRB review for all research involving human subjects at the institutions that receive *any* federal support.⁷⁰ The ANPRM points to support for legislation that would expand

65. ANPRM, *supra* note 25, at 44523. The ANPRM notes that:

The current criteria for such a waiver may not be flexible enough for dealing with a variety of circumstances, such as when Federally-sponsored research is conducted in an international setting where for cultural or historical reasons signing documents may be viewed as offensive or problematic.

Id.

66. *Id.*

67. The regulation specifies:

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in § 46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in § 46.102(e) must be reviewed and approved, in compliance with § 46.101, § 46.102, and § 46.107 through § 46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

45 CFR § 46.101(a).

68. See 21 CFR §§ 50, 56, 312, 812.

69. ANPRM, *supra* note 25, at 44528.

70. *Id.*

research oversight to all human subjects research conducted in the United States, regardless of funding source.⁷¹

III. CURRENT RESEARCH REVIEW SYSTEM CONTROVERSIES

The potential changes to the Common Rule presented in the ANPRM represent federal officials' ideas for making IRBs more efficient and effective in applying ethical principles to human subjects research. Although the ANPRM addressed many criticisms of the federal research oversight system, it ultimately suggested fairly conservative reforms, leaving important controversies untouched.⁷² Some commentators have advocated for more substantial changes. In a 2009 commentary, research ethicist Scott Kim and his colleagues argued for exempting all minimal risk research from IRB oversight.⁷³ Other scholars contend that the current system has fundamental yet remediable flaws that the ANPRM did not consider.⁷⁴ This part of the note considers examples of such concerns.

A. *Prospective Versus Retrospective Review*

In a 2012 commentary, research ethicists Robert Klitzman and Paul Appelbaum argue that a retrospective or audit-type review would be a more effective system for research oversight than the current prospective system.⁷⁵ The authors contend, since reviewers under a prospective system can evaluate only what researchers propose to do, reviewers will inevitably focus on relatively unimportant details like the wording of consent forms.⁷⁶ According to Klitzman and Appelbaum, applying prospective review to research oversight undermines the purpose of the system. In contrast, the authors suggest that using a retrospective or audit-type review would allow both reviewers and researchers to shift their

71. *Id.*; NBAC 2001, *supra* note 30, at 28.

72. *See* ANPRM, *supra* note 25.

73. Kim et al., *supra* note 40. Others have argued that problems with the human research oversight system are unfixable and even that the current system is unconstitutional. *See* Simon N. Whitney & Carl E. Schneider, *Was the Institutional Review Board System a Mistake?*, 49 *CLINICAL INFECTIOUS DISEASES* 1957 (2009); Philip Hamburger, *Getting Permission*, 101 *NW. U. L. REV.* 405 (2007).

74. Charles W. Lidz & Suzanne Garverich, *What the ANPRM Missed: Additional Needs for IRB Reform*, 41 *J.L. MED. & ETHICS* 390 (2013).

75. Robert Klitzman & Paul S. Appelbaum, *To Protect Human Subjects, Review What Was Done, Not Proposed*, 335 *SCIENCE* 1576 (2012).

76. "Because prospective review can only focus on what researchers say they will do, IRBs inevitably concentrate most of their attention on the minutiae of protocols and consent forms rather than on monitoring actual performance." *Id.* at 1576.

focus in ways that are more likely to benefit human subjects. Researchers would simply register their studies with IRBs rather than seek IRB approval before commencing the research.⁷⁷ IRBs could randomly audit protocols to ensure that researchers were complying with requirements to, for example, obtain informed consent from subjects, protect subjects' personal health information, and properly characterize research as involving more-than-minimal risk or no-more-than minimal risk.⁷⁸ Klitzman and Appelbaum further argue that a retrospective system will provide more incentives for researchers to ascertain, for example, that subjects are truly providing voluntary, informed consent since their research might be audited at any time.⁷⁹ In addition, the ethicists propose that moving to a retrospective system of ethics review would provide an opportunity to create an appellate IRB process which would improve efficiency and fairness of the system.⁸⁰

By comparison, Alex London argues that a prospective review system provides researchers with incentives to submit only their most polished protocols.⁸¹ Thus, according to London, the fact that reviewers end up spending time contemplating word choice in submitted documents only supports the notion that a prospective review system efficiently protects human subjects. The documents submitted to the IRB, London emphasizes, “*already reflect the influence of the regulatory regime.*”⁸² London contends that studies subject only to a retrospective review system

77. *Id.* at 1577.

78. *Id.* The authors further point out that some institutions have already implemented audit-type reviews of research studies and thus there is already some experience with the model. Adapting prospective review requirements, they contend, will be detrimental to progress. “Grafting some degree of retrospective review onto the current process would not address the system’s inefficiencies, including the work and delay inherent in universal prospective review, the undue weight given to written descriptions of procedures rather than actual researcher behavior, and the emphasis on speculative outcomes.” *Id.*

79. *Id.* Klitzman and Appelbaum write that:

At present, once a study is approved by an IRB, an investigator is generally not required to monitor or improve the effectiveness of the consent process or subjects’ reactions to participation. But the possibility of being audited on the basis of how well subjects understood the study or whether they were distressed by the research procedures—based on objective, validated questionnaires—would provide different incentives.

Id.

80. *Id.* The ethicists note that “[a]lthough an appeals process could be constructed in a prospective review system, a retrospective system would allow determinations based on evidence of what actually occurred, rather than fears of what might happen. That difference may increase researcher willingness to pursue an appeals process.” *Id.*

81. Alex J. London, *A Non-Paternalistic Model of Research Ethics and Oversight: Assessing the Benefits of Prospective Review*, 40 J.L. MED. & ETHICS 930, 937 (2012).

82. *Id.*

would lack the quality assurance that gives the public confidence in research and would thus result in a decrease in research participation.⁸³

In a separate criticism reviewing twenty IRB panels, Charles Lidz and Suzanne Garverich observed that reviewers never simply accept proposals as written but will request some changes even if such changes don't substantively change the proposal.⁸⁴ The more that reviewers focus on and find fault with details such as wording on forms, the argument goes, the more time and effort researchers will spend on revising their documents for IRB review rather than ensuring that potential subjects truly understand the purpose of the study, for example.

B. Analogical Reasoning and IRBs

In a 2004 law review article, Professor Carl Coleman suggests that IRBs could benefit from assessing research study protocols in a manner similar to common law reasoning by identifying relevant features of a study under consideration, finding prior studies with similar features, and then evaluating similarities and differences between the studies to determine whether the approach taken previously should be used in the study under consideration.⁸⁵ Coleman identifies a number of potential benefits to IRBs employing such an analogical approach: improving members' exercise of discretion, reducing the inconsistency of IRB evaluations, providing a general framework for evaluating new research studies and identifying best methods for risk reduction.⁸⁶ Thus, requiring IRBs to consider evaluations rendered by other IRBs will inherently enhance the diversity of reviewers assessing any given study.

83. *Id.* at 939.

84. Lidz & Garverich, *supra* note 74, at 392.

[P]rotocol reviewers never say: "There is nothing that needs to be changed about this proposal." In fact, such a review would be quite surprising because reviewers are expected to find problems. A reviewer who made such a comment would appear either not to have done the required review, or not to be very thoughtful and thorough in the analysis.

Id.

85. Carl H. Coleman, *Rationalizing Risk Assessment in Human Subjects Research*, 46 ARIZ. L. REV. 1, 28 (2004).

86. *Id.* at 34–36. Fundamentally, Coleman notes, the use of analogical reasoning "would necessarily broaden the range of perspectives incorporated into the IRB's analysis." *Id.* at 34.

C. Facilitating Ethical Research

Some critics of the current research oversight system contend that IRBs spend so much time and effort achieving compliance with federal regulations that they contribute—albeit indirectly—to unethical behavior by researchers.⁸⁷ Spellecy and May report that clinical researchers who admit to omitting information or engaging in other forms of deception when interacting with IRBs cited as reasons long review times and “lack of clarity and/or controversy about what should be subject to IRB review.”⁸⁸ The authors suggest that as IRBs spend considerable time rewording consent forms and optimizing protocols not for the purpose of enhancing protection of human subjects but simply to improve study design, they inherently contribute to the unpredictability that undermines the legitimacy of their role in the eyes of some researchers.⁸⁹

Similarly, in their study of twenty IRB panels at ten medical institutions, Lidz and Garverich observed that IRBs spent significant time discussing design methods to the exclusion of discussions on research ethics.⁹⁰ In fact, the study data revealed IRB lapses including a failure to discuss risk minimization in 21% of protocols involving more-than-minimal risk to human subjects.⁹¹ Spellecy and May argue that IRBs should not consider themselves simply protectors of human research subjects—a conclusion that may encourage creating impediments to research since “research not undertaken poses no threat of harm to [subjects]”—but as facilitators of ethical research.⁹² A shift in emphasis of the IRB role to one of facilitator, they contend, would eliminate a

87. Ryan Spellecy & Thomas May, *More Than Cheating: Deception, IRB Shopping, and the Normative Legitimacy of IRBs*, 40 J.L. MED. & ETHICS 990, 994 (2012).

88. *Id.* at 990 (citing Jim Giles, *Researchers Break Rules in Frustration at Review Boards*, 438 NATURE 136 (2005); Brian C. Martinson, Melissa S. Anderson, & Raymond DeVries, *Scientists Behaving Badly*, 435 NATURE 737 (2005)).

89. Spellecy, *supra* note 87, at 991.

90. Lidz & Garverich, *supra* note 74, at 394. While acknowledging the limitations of observational research, the authors noted that:

[W]e do know from our study that IRBs tend to spend a lot of their time discussing the appropriateness of the design and the methods of the studies that were reviewed. For example, 15.9% of the speaking turns (i.e., any time a person at the meeting says anything, we counted one speaking turn and coded it for one or more topics that the speaker discussed) in these full board meetings involved discussion of methodological issues. The academic scientists who largely populated the IRB panels we observed often discussed the scientific issues to the exclusion of research ethics; in brief, concerns about the science sometimes diverted attention away from reviewing ethics.

Id.

91. *Id.* at 393–95.

92. Spellecy, *supra* note 87, at 994.

presumption of inadequacy that the IRB might otherwise hold about the research protocol.⁹³ Furthermore, identifying IRBs as ethical research facilitators would re-direct members' focus to the Common Rule's central mandates for IRB oversight, including risk minimization and risk/benefit assessment.

D. Community Representation on IRBs

The Common Rule requires that an IRB be made up of members "with *varying backgrounds* to promote complete and adequate review of research activities." (emphasis added).⁹⁴ The regulation further specifies that "[t]he IRB shall be sufficiently qualified . . . to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects" and requires that at least one of the members be a nonscientist, one a scientist, and one a person unaffiliated with the institution.⁹⁵ In the

93. *Id.* at 994.

94. 45 CFR § 46.107. The regulation specifies:

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of its members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners or pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with the competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Id.

95. *Id.*

case of IRBs in academic settings, there is frequently only one unaffiliated member—sometimes referred to as a community member—on a board of fifteen to twenty people that is not affiliated with the institution.⁹⁶ The National Bioethics Advisory Commission (NBAC) acknowledged concerns about the disparity in community representation and others have noted that inclusion of more community members is necessary in order to increase transparency.⁹⁷ Although an unaffiliated member must be on the IRB, under current regulations that member's absence does not prohibit quorum from being met as long as a nonscientist is present.⁹⁸ Thus, IRBs can review and approve research with only institutional representation.

Other commentators have proposed requiring that more than one unaffiliated member be on an IRB and that at least one unaffiliated member be present in order for there to be a quorum.⁹⁹ NBAC emphasized that the greater the number of unaffiliated members on an IRB the less likely it would be that an institutional conflict would persist.¹⁰⁰ NBAC further urged that research subjects be represented on the IRB. The group cautioned that unaffiliated and nonscientist members may not represent the interests of subjects any better than scientists from the institution.¹⁰¹ NBAC ultimately recommended that at least 25% of an IRB's membership be collectively made up of unaffiliated members, nonscientists, and subject representatives.¹⁰² Increasing the percentage of nonscientists and unaffiliated members would be significant since psychological studies have established that a social effect exists such that members of a group

96. In the case of independent IRBs, nearly all members will be unaffiliated with the institution. For the purposes of regulatory interpretation, the corporation administering the independent IRB is an institution. Angela J. Bowen, *Models of Institutional Review Board Function*, in THE OXFORD TEXTBOOK OF CLIN. RESEARCH ETHICS 552, 554 (Ezekiel J. Emanuel et al. eds., 2008); David Forster, *Independent Institutional Review Boards*, 32 SETON HALL L. REV. 513, 513 (2002).

97. NBAC 2001, *supra* note 30, at 62; Bowen, *supra* note 96, at 554.

98. NBAC 2001, *supra* note 30, at 62.

99. Time for Reform, *supra* note 31, at 17–18.

100. “Conflicts affecting the IRB can be handled by increasing the percentage of members who do not have any direct interests in the institution. . . . Increasing the percentage of nonscientists and members who represent the views of participants can also reduce conflicts.” NBAC 2001, *supra* note 30, at 64. NBAC further noted that use of independent or fee-for-service IRBs would practically eliminate institutional conflict concerns. *Id.* at 62.

101. *Id.* at 63.

The current IRB system requires that unaffiliated and nonscientist members serve on these groups. Although each brings valuable experience, knowledge, and insight to the IRB, neither may reflect the views of the research participants. For this reason, IRBs should include members who are specifically chosen because they represent participants' interests.

Id.

102. *Id.* at 64.

will speak up more assertively if they believe someone else in the group shares their viewpoint.¹⁰³

E. U.S. Regulations and Ethical Imperialism

Although U.S. federal regulations require that research using federal funds must be reviewed by an IRB that has been approved by the U.S. Office for Human Research Protections (OHRP), the CIOMS International Ethical Guidelines require that research conducted by investigators outside of their home country be reviewed by RECs in both countries.¹⁰⁴ Some commentators contend that U.S. regulations should mirror the CIOMS guidelines and require ethical review in the country where the research is conducted as well as in the U.S.¹⁰⁵ Others argue that approval of research protocols by a U.S. IRB should be sufficient, and still others argue that an REC in the country where the research is conducted should suffice. The views represent a variety of opinions about how flexible regulations should be concerning research that is conducted outside of the country where it is sponsored. Some commentators contend that requiring strict adherence to U.S. rules is an example of ethical imperialism in the conduct of research.¹⁰⁶

In 2002, OHRP issued new rules for non-U.S. institutions seeking authorization as sites for research conducted by U.S. researchers or others using U.S. federal funds. The authorization program is called the Federalwide Assurance for International (non-U.S.) Institutions. The foreign institution must indicate on the application whether the

103. Ivor A. Pritchard, *How Do IRB Members Make Decisions? A Review and Research Agenda*, 6 J. EMPIRICAL RES. ON HUM. RESEARCH ETHICS 31, 38 (2011). Pritchard identifies what he calls “social proof” as a source by which members of a group come to agreement:

If people see that other people are doing something, they tend to believe that behavior is correct or socially acceptable. In IRB meetings, during the discussion of a research proposal or in the actual voting process, one or more IRB members may indicate how they will vote on the decision at hand . . . once that happens, the other members are in a position where they now can vote the same way, because doing so appears to be acceptable.

Id.

104. Macklin, *supra* note 2, at 716.

105. Daniel W. Fitzgerald, Angela Wasunna, & Jean William Pape, *Ten Questions Institutional Review Boards Should Ask when Reviewing International Clinical Research Protocols*, 25 IRB: ETHICS & HUM. RESEARCH 14, 14–15 (2003).

106. *Id.*; In a study commissioned by NBAC, 77% of U.S. researchers surveyed and 85% of researchers in developing countries who were surveyed recommended the use of international guidelines instead of U.S. regulations to cover joint projects. National Bioethics Advisory Council, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* 82 (2001), <https://bioethicsarchive.georgetown.edu/nbac/clinical/Vol1.pdf> [hereinafter NBAC International 2001].

Declaration of Helsinki or some other statement of ethical principles governs it in protecting the rights and welfare of human subjects involved in research.¹⁰⁷ Adherence to a statement of ethical principles is not sufficient, however. The institution applying for authorization also must comply with U.S. regulations or with alternative regulatory standards that are consistent with the U.S. Common Rule.¹⁰⁸ Additional questions surround the mechanism of ethics committee review. For example, when research protocols are reviewed by an IRB in the U.S. and an REC in the country where the research is to be conducted, how should any disagreements between the committees be resolved? Evidence suggests that U.S. IRBs rarely even try to communicate with RECs in host countries.¹⁰⁹ Various commentators have observed that the welfare of human subjects involved in research would be better protected if U.S. IRBs worked more closely with RECs in countries where U.S.-sponsored research is conducted.¹¹⁰

107. U.S. Dept. of Health & Human Servs., Office for Human Research Prots., *Federalwide Assurance Instructions*, available at <http://www.hhs.gov/ohrp/assurances/forms/fwainstructions.html>.

108. OHRP identifies the following as acceptable research standards:

45 C.F.R. § 46;

21 C.F.R. § 50 and 21 C.F.R. § 56;

International Conference on Harmonization - Good Clinical Practice E6;

Council for International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects;

Canada Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans;

Indian Council of Medical Research: Ethical Guidelines for Biomedical Research on Human Participants

See U.S. Dep't. of Health and Human Servs., Office of Human Research Prots.' International Research Standards, available at <http://www.hhs.gov/ohrp/international/index.html> (last visited Apr. 6, 2015); 45 CFR § 46.101.

109. Macklin, *supra* note 2, at 717.

110. In a 2003 review of international clinical research, Daniel Fitzgerald, Angela Wasunna, and Jean Pape noted that

IRBs from a wealthy sponsor country should ensure that a viable local ethics committee in the proposed host country will review the protocol. Further, IRBs in sponsoring countries should rely on the local ethics committee for obtaining important information about the host country.

See Fitzgerald et al., *supra* note 105, at 14. The commentators further note that "the sponsor country IRB and the local IRB may possess complementary expertise and may be able to carry out a better review working together than either could working alone." *Id.*

IV. ADDITIONAL CHANGES NEEDED

Ethical research oversight in the U.S. has occurred via IRBs for more than thirty years accompanied by very few revelations of research abuse involving human subjects. Nonetheless, researchers and other critics have assessed the current IRB system as an inefficient, bureaucratic impediment to productive research that also fails to adequately protect human subjects.¹¹¹ The ANPRM identified a number of potential reforms to federal regulations meant to improve IRB function but the suggested reforms did not go far enough. In fact, regulations by themselves cannot ensure that research is conducted according to ethical principles. It is, instead, the people applying the regulations who determine whether research is conducted according to ethical principles. This section evaluates the potential regulatory reforms and suggests additional tools that might be developed to aid IRBs in the process of providing ethical research oversight.

A. *Assessment of ANPRM Provisions*

1. *Ensuring Risk-Based Protections*

The changes contemplated by the ANPRM to expand the category of research projects that qualify for expedited review would improve the calibration of the degree of risk that research poses to the degree of research oversight. Specifically, the contemplated changes would allow research that involves no more than minimal risk to forgo full IRB review, ultimately saving time and money without sacrificing human welfare. In addition, the change would likely improve researchers' confidence in the ethics review system as researchers would be less likely to feel that their time and attention was being wasted on trying to justify trivial procedures. Particularly important to the contemplated change is the suggestion that the list of activities qualifying for expedited review would be routinely reassessed and updated, giving further credence to the notion that IRBs are reviewing studies for important ethical concerns rather than as simply a routine, bureaucratic manner.

111. Whitney & Schneider, *supra* note 28, at 398; Fost & Levine, *supra* note 40, at 2196; Hamburger, *supra* note 73, at 407.

2. Streamlining IRB Review of Multicenter Studies

The ANPRM contemplates another important change to the Common Rule in suggesting that a single IRB be utilized for multicenter domestic studies. Mandating that institutions that participate in multicenter studies select a single IRB of record would prevent an unnecessary duplication of costs. As the ANPRM suggests, individual institutions could still choose to conduct their own internal ethics review but the duplication of time and expense would probably be so obvious that the mandated selection of an IRB of record would discourage this practice, saving tremendous resources overall.

3. Improving Informed Consent

By simply acknowledging the potential conflict, the ANPRM made a critical first step in reconciling the U.S. requirement for individual informed consent and the cultural practices in communities where research may be conducted but such concepts of individual consent are not supported. Adequately addressing needed reforms to the process of obtaining informed consent, however, requires acknowledging the ways in which proposed research is likely to be received by participants in the U.S. versus other countries. For example, in some developing countries, a substantial proportion of the population may be illiterate or semiliterate; requiring subjects to sign written consent documents in such communities would clearly undermine the notion that potential subjects were providing their true informed consent.¹¹² In other communities, potential research subjects may be unfamiliar with medical research concepts that are referenced in consent documents. In its 2001 report on international research, the U.S. National Bioethics Advisory Commission (NBAC) contemplated this dilemma.¹¹³ NBAC emphasized that it was not sufficient to simply present information about the research to potential subjects but that researchers must ensure that potential subjects understood the information.¹¹⁴ Changes to the regulations requiring informed consent

112. NBAC International 2001, *supra* note 106, at 49.

113. *Id.* at 40–42. NBAC encouraged researchers to seek creative ways of presenting information that would be understood by potential research subjects, such as using analogies that are relevant to the local population. *Id.*

114. *Id.*; In its report, NBAC specifically recommended the following:

Recommendation 3.4: Researchers should develop procedures to ensure that potential participants do, in fact, understand the information provided in the consent process and should describe those procedures in their research protocols.

from human research subjects needs to account for such necessary adaptations based on differences in populations where research is performed. In some cases, it may be necessary to document informed consent in ways that have not previously been considered, including, for example, by audio or video recording. It may also be necessary to eliminate the absolute requirement for documentation of informed consent under some circumstances and instead rely on the researcher's protocols and testimony to ensure that informed consent is obtained from all research subjects.¹¹⁵

4. Expanding Federal Regulations

The expansion of federal regulations contemplated by the ANPRM would require IRB review for all research involving human subjects at research institutions that receive federal support. Unfortunately, this contemplated change does not go far enough. A further extension of federal ethics review oversight would require legislative action and should be the focus of future reform efforts in this area. After all, the level of interest in human welfare should not be dependent upon the source funding the relevant research.

B. Establish Database of IRB Experience

The suggested retrospective system of ethics review relies on the researcher to implement policies in the way that seems most appropriate to him or her. Since IRB members are frequently colleagues of the researchers whose studies they review, we would expect that IRB members already have this level of deference. However, the very fact that each consent form, promotional flier, and other documentation about a research study must be approved by the IRB undermines this sense of deference and directs the resources of both IRB members and researchers away from truly improving research studies and misdirects it to identifying inconsequential errors. Thus, a retrospective ethics review system would

Recommendation 3.5: Researchers should consult with community representatives to develop innovative and effective means to communicate all necessary information in a manner that is understandable to potential participants. When community representatives will not be involved, the protocol presented to the ethics review committee should justify why such involvement is not possible or relevant.

Id. at 42.

115. Circumstances that might warrant such treatment include research studies that qualify for expedited review conducted in communities that object to the use of recording devices.

be largely beneficial in that it would restore a sense of deference for the researcher while at the same time saving on administrative costs and IRB members' time since only a fraction of research studies involving human subjects would be reviewed.

One potential downside of adopting a retrospective review system is that it may lead to a shift away from research participation as Alex London suggests.¹¹⁶ More likely, however, there will only be a modest increase in public unease about biomedical research as a result of such change. In fact, public trust in the current review system may be misplaced since often IRBs are made up of researchers' own colleagues where incentives to approve research studies are plentiful. Instead, I propose adapting the current prospective research oversight system to include analogous review. Currently there is no mechanism for an IRB to capitalize on the collective knowledge of other IRBs when reviewing a given research study. However, the current system might be adapted such that studies are randomly selected for follow-up audit-type review. Outcomes of research studies that are reviewed retrospectively would be compared with information from the IRB's original discussion about the study and a database of such collective information could be established. Although the logistical efforts required to establish such a system would be immense, the long-term benefits would be more substantial. Even where an IRB was charged with reviewing a research protocol to which there was no comparable study in the database, there would likely still be some useful information in the database for review. For example, an entirely novel protocol might be targeted to a subject population that had been targeted by a previous study. IRB members could thus consider the review and assessment of both recruiting materials and consent documents from the original study when reviewing similar materials for the new protocol.

C. IRBs as Facilitators

As previously mentioned, studies analyzing the work of IRB panels have established that IRBs routinely fail to discuss some of the fundamental criteria for regulatory approval as they pertain to a given research study.¹¹⁷ Such criteria include risk minimization, risk/benefit comparison and data monitoring.¹¹⁸ Shifting the role of the IRB from reviewer to facilitator, as Spellecy and May suggest, will re-direct

116. London, *supra* note 81, at 939.

117. Lidz & Garverich, *supra* note 74, at 394.

118. *Id.*

members' energy and attention from details of scientific protocols and informed consent documents to discussions about research and ethics. One way of implementing such a philosophical change might be to require the IRB chairperson to open each discussion of a study with a broad question along the lines of "What is it that the researcher seeks to study? What about such a study is ethical? What might be unethical?" The IRB would thus start their discussion of the proposed research study focusing not on the specifics of the study protocols but generally on the ultimate goal of the researcher.

Another simple but effective tool to combat oversights in IRB discussions would be to provide each IRB with a standard agenda structured around the regulatory criteria for IRB approval. The agenda would aid IRB members as a visual reminder of what has and has not been discussed as they proceed through a particular review. In addition, establishing a routine for the review of each research proposal will make it less likely that any critical discussion is omitted.

D. Improve IRB Representation

Commentators on the federal oversight of human subjects research have routinely highlighted the lack of ethics education for both research investigators and IRB members as an important target for reform.¹¹⁹ An informal survey of academic and independent IRBs reveals that a number require research investigators to complete some type of ethics training prior to submitting materials for review. Ethics education requirements for IRB members, if any, are unclear. Importantly, the regulations of the Common Rule do not establish any ethics training requirements nor were any mentioned in the contemplated reforms outlined in the ANPRM. According to the regulations, however, IRBs are necessarily made up of a diverse group of people with different experience related to science, medicine, and philosophy. Requiring all IRB members to engage in ongoing ethics education programming will enable members to review and discuss research proposals with the same language in mind which is critical when considering new and complex ethical issues. Furthermore, a requirement for continuing ethics education will ensure that as knowledge about given procedures development and standards change, for instance, all IRB members have current information. In addition, changes to the Common Rule should adopt NBAC's recommendation that at least

119. NBAC 2001, *supra* note 30; Bowen, *supra* note 96, at 557.

twenty-five percent of an IRB's members be a combination of nonscientists and unaffiliated members.¹²⁰ Such an increase in diversity will lessen the likelihood of conflict of interest problems, which undermine both the system of ethical oversight and biomedical research.

Another tool for improving IRB representation is the potential for developing specialized central IRBs. Such IRBs would be made up of members with expertise in a particular type of biomedical study, the cultural norms of a given region/community, or simply with considerable experience in reviewing a certain type of research protocol that make them uniquely suited to review a given category of research proposals. The development and use of specialized IRBs would alleviate some of the burdens of overworked reviewers who often lack the time and administrative resources required to adequately familiarize themselves with uncommon research techniques or the cultural expectations of a community that is a proposed research site.

CONCLUSION

Although proposed reforms to current policies on research involving human subjects contemplate many potentially useful changes, they do not fully address the needs of an ever-evolving biomedical research world. Additional reforms that focus on establishing a means to share information between IRBs, the importance of discussions on ethics, and continuing education for IRB members are needed to improve the efficacy and efficiency of human research oversight.

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120. NBAC 2001, *supra* note 30, at 63.

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