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## Conflicting Interests & Conflicting Laws: Re-aligning the Purpose and Practice of Research Ethics Committees

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# CONFLICTING INTERESTS & CONFLICTING LAWS: RE-ALIGNING THE PURPOSE AND PRACTICE OF RESEARCH ETHICS COMMITTEES

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## I. INTRODUCTION

[I]n the early 1980s, that feeling of utter despair [felt by women diagnosed with aggressive breast cancer] started to change as women and their families began hearing of a new treatment that held out some hope.... Unfortunately, those stories of success quickly turned into a misleading bandwagon of enthusiasm. Sometimes fueled by greed and even fraud. Tragically, thousands of women were railroaded into making uninformed decisions.<sup>1</sup>

Interest in high dose chemotherapy (HDC)<sup>2</sup> was already strong when Dr. Werner Bezwoda published research results supporting the procedure in 1995.<sup>3</sup> In a 1996 publication, Dr. Bezwoda touted his research as proof that HDC was superior to conventional treatments for metastatic breast cancer.<sup>4</sup> Influenced by Dr. Bezwoda's claims, and despite the fact that other research had shown no benefit for women undergoing HDC, as many as 6,000 women a year paid between \$100,000 and \$200,000 apiece to undergo the procedure.<sup>5</sup> HDC had become big business, providing a substantial profit margin to physicians and hospitals performing the procedure.<sup>6</sup> No one wanted to question the benefits of HDC; it provided hope...and money.<sup>7</sup>

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1. *20/20 Friday: A Betrayal of Hope; Breast Cancer Patients Urged to Have Bone Marrow Transplants for Money Rather Than Better Health* (ABC television broadcast, Apr. 14, 2001) (statement made by reporter Dr. Timothy Johnson).

2. HDC treatment requires that patients have bone marrow stem cells removed from their body and stored prior to receiving extremely high doses of chemotherapy. National Women's Health Network, *High-Dose Chemotherapy Debacle Highlights Systemic Weaknesses*, 25 NETWORK NEWS 3 (2000). If the patient survives the chemotherapy regimen, the stem cells are then transplanted back into her body in an effort to restore the bone marrow that was destroyed by the chemotherapy. *Id.*

3. Thomas H. Maugh II & Rosie Mestel, *Key Breast Cancer Study was a Fraud*, L.A. TIMES, Apr. 27, 2001, at A1.

4. Michelle Marble, *Breast Cancer (Therapy): Proven Superiority of High Dose Chemotherapy for Metastatic Disease*, CANCER WEEKLY, Dec. 9, 1996, at 7-8.

5. National Women's Health Network, *supra* note 2, at 3.

6. Gina Kolata & Kurt Eichenwald, *Health Business Thrives on Unproven Treatment, Leaving Science Behind*, N.Y. TIMES, Oct. 3, 1999, at 1.

7. *Id.* See also National Women's Health Network, *supra* note 2, at 3; *20/20 Friday*, *supra* note 1 ("Doctors knew that high dose had not been defini-

Dr. Bezwoda repeated his claims again before an international conference of cancer experts in 1999.<sup>8</sup> That is when Dr. Bezwoda's claims about HDC, and his reputation as a prestigious cancer researcher, began to fall apart.<sup>9</sup> In an effort to discover why the doctor's results were so different from other research projects, several researchers asked to review Dr. Bezwoda's clinical trial data.<sup>10</sup> In doing so, they discovered that much of the data used to support HDC's effectiveness was non-existent or had been falsified.<sup>11</sup> In a 2000 letter to his former employer, the doctor claimed that he had faked his research results "in a foolish desire to make the presentation more acceptable."<sup>12</sup>

Ensuring the integrity of research projects is an increasingly prominent topic in the field of medicine.<sup>13</sup> In the last few decades, the number of medical research projects has increased exponentially.<sup>14</sup> Paralleling this increase is an expansion in the geographic locations where research projects are situated, including many new research projects conducted at international locations.<sup>15</sup> The global expansion of medical research has

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tively proven to more effective but they were under pressure to continue what by then was big business.").

8. Denise Grady, *Conference Divided Over High-Dose Breast Cancer Treatment*, N.Y. TIMES, May 18, 1999, at A19.

9. *Id.* At the conference, all of the research presented on HDC, except Dr. Bezwoda's, showed that the procedure had no benefit for patients. *Id.* As a result of this discrepancy, researchers from the United States traveled to South Africa (where Bezwoda worked at the University of Witwatersrand Medical School) to review the doctor's research data. Michael Hagmann, *Cancer Researcher Sacked for Alleged Fraud*, 287 SCIENCE 1901, 1901 (2000). Bezwoda was fired by the University shortly thereafter. *Id.*

10. Hagmann, *supra* note 9, at 1901

11. *Id.*; Maugh & Mestel, *supra* note 3.

12. *South Africa: Cancer Professor Was A Serial Fraud*, AFRICA NEWS, May 4, 2001. For a further discussion of the implications of Dr. Bezwoda's scientific misconduct, see Richard Horton, *After Bezwoda*, 355 LANCET 942, 942-43 (2000).

13. See, e.g., Chris Beyrer & Nancy E. Kass, *Human Rights, Politics and Reviews of Research Ethics*, 360 LANCET 246, 246 (2002).

14. See, e.g., Eve E. Slater, *IRB Reform*, 346 NEW ENG. J. MED. 1402 (2002). Federal funding of medical research has more than doubled since 1995; private sponsorship of research has increase at the same rate. *Id.*

15. See generally Timothy Caulfield, *Globalization, Conflicts of Interest and Clinical Research: An Overview of Trends and Issues*, 8 WIDENER L. SYMP. J. 31 (2001) (discussing general trends related to the globalization of clinical research and conflicts of interest).

prompted many new questions about how to ensure the safety of human research subjects<sup>16</sup> during clinical trials.<sup>17</sup> Concerns involving clinical trials in the United States and abroad focus on five major areas: appropriateness of research designs;<sup>18</sup> proper scientific and ethical review of research proposals;<sup>19</sup> reasonableness of participant selection;<sup>20</sup> assurance that voluntary informed consent<sup>21</sup> was obtained from all research participants;<sup>22</sup> and receipt of appropriate treatment during and after a clinical trial.<sup>23</sup> Debate over the elements of these five topics is likely to

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16. 1 NATIONAL BIOETHICS ADVISORY COMMISSION, ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES, at i (2001) [hereinafter NBAC INTERNATIONAL RESEARCH].

17. For the purposes of this Note, a "clinical trial" is defined as the administration of and intervention for diagnosis, treatment, or prevention:

The intervention could be a drug or biologic; a device; a behavioral intervention, such as counseling or education; a procedure, such as surgery, laser treatment, or a diagnostic test; or a specific service, such as home or hospice care. A clinical trial can be designed and supported for commercial reasons, such as approval of a new drug, or in response to interest by an individual investigator or research group.

INSTITUTE OF MEDICINE, RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS 34 (2002). See also *infra* Part II.A.

18. Research design includes a complete description of types or levels of treatment that will be provided to clinical trial participants and how the new treatment will be compared to existing treatment, if any exists. INSTITUTE OF MEDICINE, *supra* note 17, at 8–9.

19. Ethical review is conducted by a committee whose purpose is to evaluate whether the proposed research is ethical according to ethical guidelines for medical research. *Id.* at 13.

20. This concern relates to whether the choice to conduct a clinical trial within a particular country or population group is reasonably related to the population's health needs. *Id.* at 7–8.

21. Informed consent is a statutory and common law doctrine that requires a physician to fully disclose treatment risks and complete details of treatment procedure to patients before administering a proposed treatment. Shannon Benbow, *Conflict + Interest: Financial Incentives and Informed Consent in Human Subject Research*, 17 NOTRE DAME J.L. ETHICS & PUB. POL'Y 181, 187 (2003).

22. Concern that cultural issues can impede a participant's understanding of the clinical trial and the risks involved in becoming a participant. NBAC INTERNATIONAL RESEARCH, *supra* note 16, at 11.

23. *Id.* at 9, 12.

continue, particularly in light of ever-increasing research budgets and expansion of research into developing countries.<sup>24</sup>

A vital component of good medical research is analysis of research protocols, by an independent review body, for potential ethics violations.<sup>25</sup> In the United States, most research projects that involve human participants must be submitted to ethics review committees, called Institutional Review Boards (IRBs), for approval.<sup>26</sup> Internationally, many nations have their own regulations providing for ethical review of medical experiments through agencies and/or committees or groups generally referred to as Research Ethics Committees (RECs).<sup>27</sup> IRBs and RECs are charged with approving or denying research protocols based upon whether the proposed research is scientifically valid and whether there are adequate protections to ensure the safety and well-being of participants.<sup>28</sup>

Despite their status as the gatekeepers in the conduct of clinical trials, RECs and IRBs lack uniformity nationally and

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24. See, e.g., Trudo Lemmens & Paul B. Miller, *The Human Subject Trade: Ethical and Legal Issues Surrounding Recruitment Incentives*, 31 J.L. MED. & ETHICS 398, 401 (2003) (payment of finders fees to physicians for obtaining research participants for commercial trials may drive physicians to recruit inappropriate subjects and to be lenient with informed consent procedures); Ruqaiyah Yearby, *Good Enough to Use for Research, But Not Good Enough to Benefit from the Results of that Research: Are the Clinical HIV Vaccine Trials in Africa Unjust?*, 53 DEPAUL L. REV. 1127 (2004) (selection of research participants in Africa unjust and unethical because African populations, individual African research participants in particular, do not receive the benefits of therapies they helped to test); Jeremy Sugarman, *Lying, Cheating and Stealing in Clinical Research*, 1 CLINICAL TRIALS 475, 475-76 (2004) (discussing the considerable attention focused on the integrity of clinical research and need for clear guidance and transparency in situations involving scientific misconduct).

25. NBAC INTERNATIONAL RESEARCH, *supra* note 16, at 5.

26. See 42 U.S.C. § 289 (2005) (requires IRB approval for all research that receives government funding). See also, 21 C.F.R. § 56 (2005) (the Food and Drug Administration (FDA) requires that research on new drugs receive approval by an IRB).

27. See Robert J. Levine, *Research Ethics Committees*, in 4 ENCYCLOPEDIA OF BIOETHICS 2311 (Stephen G. Post ed., 3d ed. 2004). Different countries may use different names, and some emulate the United States by calling their review committees IRBs, but for the purposes of this Note non-U.S. review committees will be referred to as RECs.

28. See *infra* Part III.

internationally.<sup>29</sup> The IRB system in the United States is generally held out to other nations as the best existing format for ethical review of medical research.<sup>30</sup> Despite this distinction, there are minimal specific regulations or procedures that all IRBs must follow.<sup>31</sup> There is no one set of ethics guidelines that all review committees must use.<sup>32</sup> Each institution that wishes to establish an ethics review committee is required to develop many of its own guidelines and operating procedures—resulting in substantial inconsistency between institutions.<sup>33</sup> This problem only increases in magnitude for RECs in other countries that have less developed regulations and little experience managing ethics issues in medical research.<sup>34</sup>

In the last several years, one of the most highly publicized safety issues has been how best to protect participants when researchers and research institutions have personal interests that may conflict with their obligation to protect participants' safety.<sup>35</sup> However, despite heavy publicity, only minimal regu-

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29. See, e.g., Bernard M. Dickens, *The Challenge of Equivalent Protection*, in 2 NATIONAL BIOETHICS ADVISORY COMMISSION, *ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES A-10* (2001) [hereinafter 2 NBAC INTERNATIONAL RESEARCH]. Inconsistency often leads to conflicting regulations of research conducted at foreign sites, specifically when U.S. regulations are applicable due to U.S. funding or the need for FDA approval. *Id.* Determinations of when U.S. regulations are applicable to a clinical trial is discussed *infra* Part III and V.

30. Marie Hirtle et al., *A Comparative Analysis of Research Ethics Review Mechanisms and the ICH Good Clinical Practice Guideline*, 7 *EUR. J. HEALTH L.* 265, 267 (2000). See also INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, *E6 GOOD CLINICAL PRACTICE: CONSOLIDATED GUIDANCE* (1996) [hereinafter ICH GCP] (The ICH Good Clinical Practice guide adopted ERC provisions almost identical to the Common Rule (*infra* Part III)), available at <http://www.fda.gov/cder/guidance/959fnl.pdf> (last visited Feb. 16, 2005).

31. See *infra* Part V.

32. See *infra* Part II.

33. See *infra* Part V.

34. See DHHS OFFICE OF INSPECTOR GENERAL, *THE GLOBALIZATION OF CLINICAL TRIALS: A GROWING CHALLENGE IN PROTECTING HUMAN SUBJECTS* 15 (2001) [hereinafter *GLOBALIZATION OF CLINICAL TRIALS*] (noting that sponsors of clinical research have concerns about the adequacy of review by RECs in nations with little experience conducting medical research).

35. See, e.g., Pamela R. Ferguson, *Legal and Ethical Aspects of Clinical Trials: The View of Researchers*, 11 *MED. L. REV.* 48, 51–52 (2003). Conflicts of interest are discussed in detail in Part IV of this Note.

latory guidance has occurred.<sup>36</sup> Regulatory changes to the mandatory functions of RECs—specifically, changes to U.S. regulations—can minimize the risk of unethical research occurring in the United States and other nations. International collaboration on development of uniform, internationally-accepted regulations for RECs has been initiated by a few nations, but remains limited.<sup>37</sup> Conflict of interest policies implemented in conjunction with REC oversight can strengthen the ethical review process and promote the purpose of ethical review—participant safety and well-being.

This Note posits that substantive and procedural weaknesses in the operations of ethical review committees should be amended, through revision of U.S. regulations for national and foreign clinical trials, in order to develop consistent policies for the management of conflicts of interest and enhance the protection of research participants. Part II provides an overview of bioethics and clinical trials, including several influential ethics guidelines that have directed post-World War II medical research. Part III gives a general overview of ethical review committees in the United States and abroad. This Part includes information on the different control mechanisms used within the United States to regulate IRBs. This Part also examines control mechanisms for RECs in other countries. Part IV investigates the issue of conflict of interest as it relates to medical research and clinical trials at the national and international level. Part V proposes regulatory solutions to clarify the role of IRBs and RECs and ameliorate deficiencies that currently exist in the regulation of conflicts of interest. Specifically, this Part suggests several regulatory changes that, if implemented, have the potential to increase national and international ethical review committees' ability to fulfill their purpose of ensuring participant safety by providing them with *all* the information important for evaluating research proposals.

## II. BIOETHICS

Historically, many cultural groups believed that illness stemmed from violations of social or natural law, and that the methods of the healer must be “right” and “good” in order to

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36. See *infra* Part V.

37. See *infra* Part II.B.2.



return health to the sick person.<sup>38</sup> Over the last twenty-five centuries, ethics in Western countries has been consistently linked to the moral beliefs of Western society.<sup>39</sup> Bioethics is the study and evaluation of the moral duties, obligations and principles governing the actions of individuals and groups within the medical field.<sup>40</sup> The term “bioethics” was originally coined by a Wisconsin cancer researcher and was intended to encompass the ethical review of all biological sciences, such as ecology, agriculture and medicine.<sup>41</sup> However, the term “bioethics” is now synonymous with biomedical ethics and generally only covers issues in biomedical research, medicine and health care.<sup>42</sup> The study and practice of bioethics includes a variety of professional backgrounds—including philosophers, theologians, attorneys, clinicians, and researchers—with each providing a unique perspective on the moral obligations of caregivers and researchers toward patients.<sup>43</sup>

The import of bioethics has continued to grow over the last few decades, reflecting the vast increase and complexity of modern medical advances and the policy questions those advances raise for governments, medical professionals, and the public.<sup>44</sup> In the United States, the field of bioethics developed into a major area of academic discourse following revelations of several highly questionable research experiments during the late 1960s and early 1970s,<sup>45</sup> including the infamous Tuskegee syphilis

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38. ALBERT R. JONSEN, *THE BIRTH OF BIOETHICS* 5–6 (1998).

39. *Id.* at 6.

40. *See, e.g.*, LAWRENCE O. GOSTIN, *PUBLIC HEALTH LAW AND ETHICS* 10 (2002).

41. OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS, *BIOMEDICAL ETHICS IN U.S. PUBLIC POLICY—BACKGROUND PAPER 2* (1993) [hereinafter *OTA BIOMEDICAL PAPER*] (Report # OTA-BP-BBS-105), available at <http://www.wws.princeton.edu/cgi-bin/byteserv.prl/~ota/disk1/1993/9312/9312>.

PDF (last visited Feb. 16, 2005). The term “bioethics” was coined by Van Rensselaer Potter (1911-2001), a biochemist who worked as a professor of oncology at the University of Wisconsin. *Id.* at 2 (citing VAN RENSSELAER POTTER, *BIOETHICS: BRIDGE TO THE FUTURE* (1971)).

42. *Id.*

43. *Id.*

44. *Id.* Publicity surrounding cloning, euthanasia, stem-cell research, and other new medical advances has increased public awareness of bioethical issues, which in turn has led to increased governmental regulations and guidelines. *See, e.g.*, Ferguson, *supra* note 35, at 52–54.

45. OTA BIOMEDICAL PAPER, *supra* note 41, at 2.

study<sup>46</sup> and government-sponsored radiation experiments.<sup>47</sup> Modern bioethical topics are varied and include such issues as

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46. See, e.g., Allan M. Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Experiment*, in *TUSKEGEE'S TRUTHS* (Susan M. Reverby ed., 2000). For forty years, between 1932 and 1972, the U.S. Public Health Service (PHS) conducted an experiment on 400 black men with late stage syphilis. *Id.* at 15. These men, for the most part illiterate sharecroppers from Macon County in Alabama, were never told what disease they were suffering from or of its seriousness. *Id.* at 18, 21. As a means to enroll participants, the research subjects were told they would be treated for "bad blood," the local term used to describe syphilis. *Id.* at 22. However, doctors never intended to cure the men's syphilis, but rather intended to withhold all forms of treatment so they could analyze the natural progression of syphilis over time. *Id.* at 18. The experiment's data was to be collected from autopsies of research subjects, and thus the men were deliberately left to degenerate under the ravages of tertiary syphilis, which can include tumors, heart disease, paralysis, blindness, insanity, and death. *Id.* at 23. "As I see it," one of the doctors involved explained, "we have no further interest in these patients until they die." *Id.* Researchers continued to withhold treatment for the men throughout the forty years of the study. *Id.* at 25. The men were prevented from participating in several nationwide campaigns to eradicate venereal disease. *Id.* at 26. When penicillin was discovered in the 1940s—the first real cure for syphilis—the Tuskegee men were deliberately denied the medication. *Id.* at 27. By the end of the experiment, twenty-eight of the men had died directly of syphilis and more than one hundred were dead of related complications. *Id.* at 15.

47. See generally OFFICE OF HUMAN RADIATION EXPERIMENTS, U.S. DEP'T OF ENERGY, HUMAN RADIATION EXPERIMENTS: THE DEPARTMENT OF ENERGY ROADMAP TO THE STORY AND THE RECORDS (1995), available at <http://tis.eh.doe.gov/ohre/roadmap/roadmap/index.html> (last visited Feb. 2, 2005). From 1945 until 1974, the U.S. government funded multiple research projects on the effects of radioactive substances on the human body. *Id.* Patients were injected with varying doses of uranium, plutonium, and other radioactive elements to determine the physiological effects these substances have on the body. *Id.* These experiments took place throughout the country and were run by government agencies, the military, as well as publicly-funded hospitals and other research programs. *Id.* Unlike the vast majority of medical research projects, federally-funded human radiation experiments were deemed "classified," and all procedures and results were held in secret by the U.S. Government. *Id.* As a result, decisions on proper conduct of research by higher authorities were never shared with the personnel actually conducting the experiments and there was little to no guidance to researchers on what ethical guidelines should have been followed. *Id.* The records on these experiments, since de-classified, suggest that many research participants did not consent to being a part of the radiation experiments. *Id.* Additionally, there is substantial question as to the value of some of the treatment protocols undergone by participants, i.e. some experiments were done to further scientific knowledge rather than to provide an form of treatment to the patient. *Id.*

abortion, euthanasia, organ transplantation, cloning and stem-cell research.<sup>48</sup>

### A. Clinical Trials

This Note will focus solely upon one of the many topics that fall within the field of bioethics, the ethics of clinical trials conducted with human participants. To better understand the ethics that are applied to clinical trials, it is important to understand the trials process. First, it is important to note that there are several different types of clinical trials, each having a different objective.<sup>49</sup> Many clinical trials have treatment objectives and test new drugs, medical devices or surgical therapies.<sup>50</sup> Other types of trials include prevention trials, diagnostic trials, screening trials and quality of life trials.<sup>51</sup> This Note will focus its attention upon the process involved in treatment trials.

A second important fact is that clinical trials occur in a series of progressive steps, with each step building upon the information learned in the previous step.<sup>52</sup> The first step in the clinical trials process is to determine whether the new drug compound or other product is safe for use with humans.<sup>53</sup> This part of the

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48. OTA BIOMEDICAL PAPER, *supra* note 41, at 2–3.

49. National Library of Medicine, An Introduction to Clinical Trials, ClinicalTrials.gov website, at <http://clinicaltrials.gov/ct/info/whatis.jsessionid=EA61A759F5AD0B1BF685C3714332AD76> (last visited Jan. 26, 2005).

50. *Id.* Treatment trials generally look at “experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.” *Id.*

51. *Id.* Prevention trials are aimed at increasing our ability to prevent occurrence or recurrence of disease. *Id.* Diagnostic trials are designed to improve a medicine’s ability to diagnose a particular disease or condition through improved testing or medical procedures. *Id.* Screening trials seek new or better ways to detect diseases or other medical conditions. *Id.* Quality of Life trials, also known as Supportive Care trials, are intended to improve the quality of life for patients who suffer chronic illnesses. *Id.*

52. *See, e.g.,* CenterWatch, *Free Research Information*, Books & Publications, CenterWatch Clinical Trials Listing Service, at <http://www.centerwatch.com/bookstore/freeresearch.html> (last visited Jan. 26, 2005) (discussing the phases of clinical testing that normally occur with experimental drugs).

53. *See, e.g.,* International Conference on Harmonization; Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. 66,113, 66,115 (Dec. 17, 1997) (guidance published by the FDA setting forth general scientific principles for the conduct, performance and control of clinical trials).

process is called pre-clinical research (or non-clinical studies).<sup>54</sup> After a new product has been developed, it must be tested on two or more non-human species of animals (one rodent, one non-rodent) to determine if it is safe to give the same product to humans.<sup>55</sup> These safety evaluations are important for determining whether the product can be used at all, or whether specific limitations should be placed upon the product's use in humans.<sup>56</sup> This initial step can take a few weeks to several years.<sup>57</sup>

Once pre-clinical research has shown that a product can be safely<sup>58</sup> tested on humans, the clinical trial process begins in earnest. The steps in the clinical trial process are often referred

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54. See, e.g., *id.*; CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD & DRUG ADMINISTRATION, CDER HANDBOOK 5 (1998) [hereinafter CDER HANDBOOK] (includes chapter on the processes involved in new drug development and review), available at <http://www.fda.gov/cder/handbook/> (last visited Feb. 16, 2005).

55. CDER HANDBOOK, *supra* note 54, at 6. Testing must be done on more than one species because different species may have different reactions to the product. *Id.* For pharmaceuticals, non-clinical studies usually include: "single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies, and for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential." INTERNATIONAL CONFERENCE ON HARMONIZATION, GUIDANCE FOR INDUSTRY: M3 NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS FOR PHARMACEUTICALS 2 (1997) [hereinafter ICH NONCLINICAL SAFETY STUDIES]. Other studies include pharmacology safety assessments and studies on absorption, distribution, metabolism and excretion (pharmacokinetics). *Id.*

56. See, e.g., ICH NONCLINICAL SAFETY STUDIES, *supra* note 55, at 2. For a pharmaceutical product:

The goals of the nonclinical safety evaluation include: a characterization of the toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. This information is important for the estimation of an initial safe starting dose for the human trials and the identification of parameters for clinical monitoring of potential adverse effects.

*Id.*

57. CDER HANDBOOK, *supra* note 54, at 6.

58. The fact that a product has been deemed safe to test on humans does not mean that research participants are not at risk for adverse effects. National Library of Medicine, *supra* note 49, at *Risks*. Rather, it means that the data from pre-clinical research shows that the risks are low and that the proposed benefit of the product outweighs any potential risk. CDER HANDBOOK, *supra* note 54, at 7.

to as “phases,” though labels differ in different regions.<sup>59</sup> Clinical trials of new drugs, one of the most common types of treatment trials, provide a good example of trial phases. The initial testing of the product on humans, called Phase I trials, are conducted with a small group of volunteers.<sup>60</sup> Phase I trials are used to identify side effects, support earlier determinations that the product is safe for human use, and to find a safe dosage range.<sup>61</sup> Once the process moves on to Phase II trials, the number of participants expands (generally 100–300 people) and researchers do further evaluations of effectiveness and safety.<sup>62</sup> Phase II trials are usually the initial stage where the product is tested on individuals who have the disease or medical condition that the product is designed to treat.<sup>63</sup> The number of people that the product is tested on increases into the thousands for Phase III trials.<sup>64</sup> Phase III trials are often used to compare a new treatment to existing treatments, to monitor side effects, and to confirm effectiveness of the product for its intended purpose.<sup>65</sup> After the conclusion of Phase III trials, a product that has proven itself safe and effective is generally approved for sale to the public.<sup>66</sup>

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59. See, e.g., CDER HANDBOOK, *supra* note 54, at 8–9; International Conference on Harmonization; Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. at 66,115–66,117.

60. National Library of Medicine, *supra* note 49, at *What Are the Phases of Clinical Trials?*. Initial testing is generally done on a group of twenty to eighty volunteers. *Id.* Volunteers in Phase I trials may be patients; however, they are usually healthy individuals. CDER HANDBOOK, *supra* note 54, at 8.

61. National Library of Medicine, *supra* note 49, at *What Are the Phases of Clinical Trials?*.

62. *Id.*

63. CDER HANDBOOK, *supra* note 54, at 8.

64. *Id.* at 9.

65. National Library of Medicine, *supra* note 49, at *What Are the Phases of Clinical Trials?*.

66. See, e.g., International Conference on Harmonization; Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. at 66,117. Further testing of the product often occurs after it has been marketed to the public. *Id.* These tests, known as Phase IV trials, are not considered necessary for approval of the product but may be important for making further determinations of the best dosage and optimizing the product's use. *Id.*

*B. Ethics in Human-Subject Clinical Trials*

One of the first questions many clinical trial participants ask is: “Is someone going to make sure that my safety is protected?”<sup>67</sup> To protect the safety and well-being of clinical trial participants, all research done on human-subjects is governed by one or more ethical codes.<sup>68</sup> One of the first texts dealing directly with ethics in medical practice was written in 1803.<sup>69</sup> *Medical Ethics*, written by the English physician Thomas Percival, covered traditional medical decorum regarding physicians’ relations with their patients, as well as physician-physician relationships.<sup>70</sup> Percival believed adherence to proper ethical decorum would render the profession worthy of the public’s trust.<sup>71</sup> Ethics as a guide to decorum continued through the 1940s; however, medical ethics changed significantly in the decades following World War II.<sup>72</sup> The following sections discuss the post-World War II documents on ethics in medical research that have been most widely accepted by the international community.

1. Internationally-Recognized Ethics Guidelines—  
1940 to 1980

*a. Nuremberg Code*

While medical research on humans is nothing new, the horrific experiments conducted on prisoners in Nazi concentration camps pushed ethics to the forefront of research discussions.<sup>73</sup> In *United States v. Brandt*, the first case heard before the Military Tribunal on War Crimes at Nuremberg, often referred to as the “Medicine Case,” ten criteria for ethical and humane treat-

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67. See, e.g., National Library of Medicine, *supra* note 49, at *How is the Safety of Participants Protected?*.

68. *Id.*

69. JONSEN, *supra* note 38, at 7.

70. *Id.* Physician were to be comforting, firm, gentle and discrete with patients. *Id.* Physician-physician relationships refers to the professional manner in which physicians are expected to interact with one another, in particular the showing of respect between colleagues. *Id.*

71. *Id.*

72. *Id.* at 11. One known exception to this general assertion is a 1900 book vilifying unethical Russian experimentation. *Id.*

73. See, e.g., Benbow, *supra* note 21, at 185–86.

ment of research subjects were outlined as part of the final judgment.<sup>74</sup> Those ten criteria became known as the Nuremberg Code (Code),<sup>75</sup> one of the most cited codes for ethical research.<sup>76</sup>

Analysis of the Code requires some knowledge of the Medicine Case and the experiments that were its core. The Medicine Case was conducted under U.S. military auspices at the Palace for Justice in Nuremberg, Germany.<sup>77</sup> Twenty-three defendants, all physicians but one, were tried by the tribunal; seven were sentenced to death for war crimes and crimes against humanity.<sup>78</sup> The research done by the Nazi physicians included

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74. The Medicine Case, in 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW No. 10, at 181–82 (1949).

75. The ten principles laid out by the court in its final ruling, later called the Nuremberg Code, were held by the military tribunal as the minimum necessary to satisfy moral, legal and ethical responsibilities. *Id.* The primary emphasis of the Code was voluntary consent:

[P]ersons involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

*Id.* The other nine tenets of the Code directed that experiments were to be conducted only for the good of society, they needed to be unprocurable by other methods or means of study, and must not be random or unnecessary. *Id.* Physical and mental suffering and injury to research participants was to be avoided. *Id.* Researchers were not to conduct any experiments that they believed may lead to the death or disabling of research participants. *Id.* The degree of risk to research participants was never to exceed that determined by the humanitarian importance of the problem to be solved by the experiment, i.e., if the risk to participants was high, then the gain to society from the experiment must also be very high. *Id.* As well, experiments were only to be conducted by qualified scientific personnel who could ensure that the “highest degree of skill and care” would be used during all stages of an experiment. *Id.*

76. Beyrer & Kass, *supra* note 13, at 247.

77. THE NAZI DOCTORS AND THE NUREMBERG CODE 4 (George J. Annas & Michael A. Grodin eds., 1992) [hereinafter NAZI DOCTORS].

78. *Id.*

both war-related and non-war-related activities.<sup>79</sup> Research subjects were given no choice about their participation, nor were they given any choice in any matters affecting their health and well-being. Subjects were selected from prisoners in the concentration camps—men, women and children—by soldiers or physicians without being told what was going to happen to them.<sup>80</sup> The research subjects endured extremely painful and denigrating experiments.<sup>81</sup> Many research subjects died.<sup>82</sup>

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79. See generally Eva Mozes-Kor, *The Mengele Twins and Human Experimentation: A Personal Account*, in NAZI DOCTORS, *supra* note 77, at 54. The author and her twin sister were research subjects used by Dr. Josef Mengele at the Birkenau concentration camp. *Id.* Mengele considered twins the perfect research subjects; one child to experiment upon and one child to act as the control. *Id.* Mengele used the twins for two research programs: one program dealing with genetics and the other dealing with germ warfare. *Id.* at 55. The germ warfare experiments consisted of injecting one twin with a biological agent used for germ warfare. *Id.* When the child died from the injected agent, his or her twin was then killed in order for the doctors to compare the infected versus healthy organs of the two children at autopsy. *Id.* at 56. Cross-transfusions and castrations were performed on twins to determine if an individual's sex was interchangeable, as well as other experiments to determine how the human body could be manipulated—including experiments to determine how much blood children could have removed from their body before they died. *Id.* at 57. Genetic experiments on individuals with physical abnormalities or defects were performed to determine causation. *Id.* Dr. Mengele's genetic experiments were particularly focused on means to "purify" the Aryan race. *Id.*

80. *Id.* at 55–58.

81. Telford Taylor, *Opening Statement of the Prosecution December 9, 1946*, in NAZI DOCTORS, *supra* note 77, at 67. The U.S. prosecutor's opening statement provided a detailed description of twelve research activities for the court to consider as crimes against humanity. *Id.* at 70–85. The experiments included high-altitude experiments in which prisoners were provided with gas masks and placed in a chamber that was pressurized to simulate high altitude (one experiment used pressure for an elevation of 47,000 feet); once the chamber was fully pressurized, the gasmask was removed and the reactions of prisoners were observed until they died. *Id.* at 70–72. The subjects died in excruciating pain in a process that took more than half an hour. *Id.* The researchers joked in their communiqués that any subject who survived the experiments should be pardoned to life in prison. *Id.* The freezing experiments required prisoners to stand naked outside in freezing temperatures for nine to fourteen hours or to sit in tanks of iced water for three or more hours. *Id.* at 73. In the mustard gas experiments, researchers intentionally wounded prisoners and then the wounds were infected with mustard gas. *Id.* at 75–76. Other subjects were forced to inhale mustard gas, swallow it in liquid form, or were injected with the liquid form. *Id.* at 77. One of the most extensive experiments was on sterilization. *Id.* at 82–85. The sterilization experiments



As a result of these atrocities, the Code focused upon protections that would clearly enunciate that the Nazi experiments were unethical. Therefore, the primary tenet of the Code is voluntary informed consent of research participants: "the voluntary consent of the human subject is absolutely essential. This means that the persons...should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion."<sup>83</sup> The Code also emphasizes that research participants rights and well-being must be protected.<sup>84</sup> The Nuremberg Code, heavily influenced by the United States,<sup>85</sup> became the stepping stone to the ethics guidelines used in medical research throughout the world today.

*b. Declaration of Helsinki*

The World Medical Association (WMA) is an international not-for-profit organization founded in 1947 to represent physicians around the world.<sup>86</sup> In the summer of 1964 in Helsinki, Finland, the WMA officially adopted the "Ethical Principles for Medical Research Involving Human Subjects."<sup>87</sup> This document, known as the Declaration of Helsinki (Declaration), is the most influential international protocol to emerge since the Nurem-

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were developed to find an inexpensive and quick method of sterilization that could be used "to wipe out Russians, Poles, Jews," and other undesirables. *Id.* Sterilization techniques included injection with test drugs, surgical castration, and high-dose radiation through X-rays to the genitals. *Id.* Nazi doctors also conducted experiments with malaria, Sulfanilamide, drinking sea-water, infection with typhus, epidemic jaundice, poisoning with various poisons, and experiments in which prisoners were intentional burned with the chemicals from English incendiary bombs. *Id.* at 70–85.

82. *Id.* at 70–85.

83. The Medicine Case, *supra* note 74, at 181.

84. *Id.*

85. The U.S. government and the American Medical Association (AMA) heavily influenced the Code. JONSEN, *supra* note 38, at 135. Specifically, the language of the Nuremberg Code was drawn from an ethics report to the AMA by Dr. Andrew C. Ivy, the man later chosen by the United States to act as the prosecution's medical expert during the trial. *Id.*

86. WORLD MEDICAL ASSOCIATION, ABOUT THE WMA, at <http://www.wma.net/e/about/index.htm> (last visited Feb. 27, 2005).

87. WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1989) [hereinafter 1989 DECLARATION].

berg trials.<sup>88</sup> The Declaration's introduction heavily emphasized that the primary duty and obligation of all physicians is the health and welfare of patients.<sup>89</sup> The Declaration also emphasizes that the only legitimate purpose of biomedical research involving human subjects is to "improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease."<sup>90</sup> One of the most noticeable stylistic differences between the Code and the Declaration is the placement of informed consent guidelines. Unlike the Code, the Declaration places informed consent in the middle of the document rather than as the primary tenet.<sup>91</sup> The difference reflects the Declaration authors' belief that "the essence of research ethics is the integrity and vigilance of the investigator."<sup>92</sup>

Since its adoption in 1964, the Declaration of Helsinki has been amended five times.<sup>93</sup> The Declaration of Helsinki was substantially revised in 1975<sup>94</sup> from five to twelve basic guiding principals for ensuring ethical research.<sup>95</sup> It was amended

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88. John Harris, *Research on Human Subjects, Exploitation, and Global Principles of Ethics*, in 3 LAW AND MEDICINE 379, 384 (2000).

89. The Declaration begins by declaring that,

[i]t is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission...The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

1989 DECLARATION, *supra* note 87.

90. *Id.* Aetiology is defined as "the cause of a disease." Webster's Online Dictionary, at <http://www.websters-online-dictionary.org> (last visited Feb. 5, 2005). Pathogenesis is the origin or development of a disease. *Id.*

91. JONSEN, *supra* note 38, at 136.

92. *Id.*

93. 1989 DECLARATION, *supra* note 87.

94. Heidi P. Forster et al., *The 2000 Revision of the Declaration of Helsinki: A Step Forward or More Confusion*, 358 LANCET 1449, 1449 (2001).

95. Rebecca A. Finkenbinder, Comment, *New Recommendations on International Research: Can Minimum Standards Prevent the Exploitation of Vulnerable Human Subjects in Developing Countries?*, 21 PENN. ST. INT'L L. REV. 363, 373 (2003).

again in 1983, 1989, 1996, and 2000.<sup>96</sup> The Declaration's 1983 and 1989 versions are currently codified in the Code of Federal Regulations for the U.S. Food & Drug Administration (FDA).<sup>97</sup> The 2000 revision of the Declaration includes the most substantial revisions since the 1975 amendment.<sup>98</sup> These revisions have been highly criticized due to the hasty passage of the new Declaration and because of the controversial nature of several additions.<sup>99</sup> Currently, the FDA has declined to include the 2000 Declaration in its regulations and has retained the 1989 version.<sup>100</sup> Part V of this Note discusses specific provisions within the 2000 Declaration in further detail.

*c. Belmont Report*

The majority of modern bioethics guidelines have been created by international committees; however, the guidelines formulated specifically for U.S. researchers have been highly influential at the international level. The National Research Act (Act) was signed into law by President Nixon in July 1974.<sup>101</sup> The Act was the first U.S. legislation to include medical ethics principles as a regulatory mechanism for controlling and sanctioning behavior.<sup>102</sup> The legislation promulgated by the Act cov-

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96. WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2000) [hereinafter 2000 DECLARATION].

97. 21 C.F.R. 312.120(c)(4) (codifies 1989 Declaration for foreign clinical trials of new drugs); 21 C.F.R. 814.15(b) (codifies 1983 Declaration for foreign trials of medical devices).

98. Forster, *supra* note 94, at 1449.

99. Only two weeks were made available for comments on the proposed revisions before the assembly voted. *Id.* Some of the new additions included requiring disclosure of conflicts of interest, expansion of the definition of vulnerable populations that necessitate special protections, and a requirement that research participants be assured access to best proven methods of treatment identified by the study. *Id.*

100. FDA, GUIDANCE FOR INDUSTRY: ACCEPTANCE OF FOREIGN CLINICAL STUDIES 2 (2001) [hereinafter FDA GUIDANCE REPORT], available at <http://www.fda.gov/cber/gdlns/clinical031301.pdf> (last visited Feb. 27, 2005). The FDA report did not explain why the revised Declaration was not implemented other than to note that the agency was reviewing its regulations to determine whether changes were necessary. *Id.*

101. National Research Act of 1974, Pub. Law 93-348, § 201, 88 Stat. 342 (codified as amended in scattered sections of 42 U.S.C.).

102. JONSEN, *supra* note 38, at 99.

ers all biomedical research performed by individual researchers or institutions that receive federal funding for their work.<sup>103</sup> Additionally, the Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission).<sup>104</sup> One of the mandates for the National Commission was to “identify the ethical principles which should underlie the conduct of biomedical and behavioral research with human subjects and develop guidelines that should be followed in such research.”<sup>105</sup>

Despite the existence of internationally-accepted bioethics guidelines, such as the Nuremberg Code and the Declaration of Helsinki, the National Commission determined that ethical guidelines of the time did not have sufficient depth.<sup>106</sup> The National Commission therefore commenced a series of meetings that culminated in the publication of the *Belmont Report* in April 1979.<sup>107</sup> The *Belmont Report* contained the National Commission’s recommendations for ethical principles that should be used by researchers and institutions receiving federal funding.<sup>108</sup>

The *Belmont Report* was designed as a general policy statement that provides a basic framework for discussions on biomedical research ethics.<sup>109</sup> The National Commission determined that ethical research on human subjects included three overriding principles: respect for persons, beneficence and justice.<sup>110</sup> Respect for persons incorporates protection for the autonomy of individuals and protections for individuals with

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103. *Id.*

104. National Research Act § 201.

105. JONSEN, *supra* note 38, at 102 (quoting National Research Act of 1974).

106. *Id.* The authors of the Belmont Report also determined that the Nuremberg Code and the 1975 Declaration of Helsinki were often inadequate to cover complex situations and at times were in conflict with one another. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 3 (1979) [hereinafter BELMONT REPORT], available at [http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4066b1\\_22\\_Belmont%20Report.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4066b1_22_Belmont%20Report.pdf) (last visited Feb. 27, 2005).

107. JONSEN, *supra* note 38, at 102.

108. DENNIS M. MALONEY, PROTECTION OF HUMAN RESEARCH SUBJECTS: A PRACTICAL GUIDE TO FEDERAL LAWS AND REGULATIONS 20 (1984).

109. *Id.* at 21.

110. BELMONT REPORT, *supra* note 106, at Basic Ethical Principles.

diminished autonomy.<sup>111</sup> The regulatory structure that insures respect for persons is informed consent.<sup>112</sup> Beneficence is the obligation placed upon researchers to “(1) do no harm and (2) maximize possible benefits and minimize possible harms” to participants.<sup>113</sup> The application of the beneficence principal is exemplified by thoughtful and thorough assessment of the risks and benefits associated with proposed research by investigators and IRBs/RECs.<sup>114</sup> The final overriding principal of ethical re-

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111. *Id.* In discussing the respect for persons, the National Commission defined an autonomous individual as a person “capable of deliberation about personal goals and of acting under the direction of such deliberation.” *Id.* Respect for individual autonomy recognizes the rights of individuals to have opinions and to make their own choices, so long as there is no detriment to others. *Id.* Individuals with diminished autonomy are children, those who have been incapacitated by physical or mental illness, or those whose liberty is severely limited (generally, prisoners). *Id.*

112. *Id.* at Applications. The application of respect for persons was broken down into three necessary requirements for informed consent: information, comprehension and voluntariness. *Id.* “Information” requires that individuals are provided sufficient information to make an informed opinion and choices about participation in a research project. *Id.* Sufficient information generally includes: research procedure, purpose of the research, anticipated benefits and potential risks, alternative procedures or treatments available, and “a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research.” *Id.*

113. *Id.* at Basic Ethical Principles. The National Commission noted that this principle extends to the entire enterprise of research, and thereby places an obligation on society at large as well as on individual researchers. *Id.* It was also noted that there are some inherent difficulties in implementation. *Id.* It is difficult to avoid harm when researchers are often unaware of potential harms. *Id.* It is normal in research for there to be some risk of harm to participants; the difficulty for individuals and society lies in determining what constitutes a justifiable risk. *Id.*

114. *Id.* at Applications. Risk/Benefit assessment requires that researchers carefully sift through all existing, relevant data to determine potential risks and to evaluate alternative methods of obtaining the same benefits sought in the research. *Id.* Risk/benefit analysis is a means of examining the design of proposed research and to evaluate whether risks inherent to the research are justifiable. *Id.* Justifiability of research must, at minimum, reflect the following:

- (i) Brutal or inhumane treatment of human subjects is never morally justified....
- (ii) Risks should be reduced to those necessary to achieve the research objective....
- (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk....
- (iv) When vulnerable populations are involved in research, the appropriateness of involving

search is justice.<sup>115</sup> Justice revolves around the concept of equal distributions of burdens and benefits.<sup>116</sup> Application of the justice principal results in the development of fair procedures and outcomes in the selection of research participants.<sup>117</sup> Despite being written almost thirty years ago, the *Belmont Report* retains substantial influence on U.S. research policy and later international ethics guides.<sup>118</sup>

## 2. Internationally-Recognized Ethics Guidelines— 1980 to Present

### *a. CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects*

The Council for International Organizations of Medical Sciences (CIOMS) is an international nongovernmental organization founded in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Sci-

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them should itself be demonstrated.... (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

*Id.*

115. *Id.* at Basic Ethical Principles.

116. *Id.* The burden of research, the risks to individual participants, should not fall unfairly or unequally on any one group or population of people. *Id.* Additionally, the benefits derived from research, new techniques, or drugs should not go unequally to financially or socially advantaged groups or populations. *Id.*

117. *Id.* at Applications. Both social and individual justice are relevant to the discussion of equitable selection of research participants. *Id.* Individual justice requires fairness and unbiased selection of participants. *Id.* Social justice requires awareness of those who should or should not be allowed to participate in research based on a person's ability to bear burdens or on the appropriateness of potentially increasing the burden on an already burdened class of individuals. *Id.*

118. MALONEY, *supra* note 108, at 20. A direct example of this influence can be found in the CIOMS Guidelines, *infra* Part II.B.2.i. The CIOMS Guidelines specifically identify the three overriding principles of the Belmont Report as the ethical principles that were foundational to the CIOMS Guidelines. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES, INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, at General Ethical Principles (2002) [hereinafter CIOMS Guidelines], available at [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm) (last visited Feb. 2, 2005).

entific and Cultural and Organization (UNESCO).<sup>119</sup> CIOMS began its work on ethics in biomedical research in the late 1970s.<sup>120</sup> The goal of the organization was to create a set of guidelines that would “indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set for the in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements.”<sup>121</sup>

Several bioethical documents regarding medical research have been created by CIOMS. In 1982, CIOMS, in collaboration with WHO, published *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Proposed Guidelines).<sup>122</sup> Proposed Guidelines was the first document specifically designed to help countries, developing countries in particular, effectively apply the ethical guidelines in the Declaration to their existing socio-political structure.<sup>123</sup> In 1993, revision of the Proposed Guidelines resulted in publication of *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.<sup>124</sup> Rapid changes in medical research—including the increased use of controlled clinical trials in developing countries, funded and conducted by external sponsors and investigators—required that the document receive further amendment.<sup>125</sup> The revised *International Ethical Guidelines for Biomedical Research Involving Human Subjects* was published in 2002 (2002 Guidelines).<sup>126</sup>

The 2002 Guidelines were heavily reviewed and influenced by the international community. Extensive opportunities for input by members of the international bioethics debate were provided over the four years, from 1998 to 2002, during which the revised

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119. CIOMS Guidelines, *supra* note 118, at Background.

120. *Id.*

121. *Id.*

122. *Id.* Proposed Guidelines was created prior to the outbreak of the HIV/AIDS pandemic and the subsequent large-scale research trials that were required to deal with HIV/AIDS. *Id.* It was specifically targeted toward protection of research participants in developing nations who were involved in traditional small-scale, publicly-funded research protocols. *Id.*

123. *Id.*

124. *Id.*

125. *Id.* See *infra* Part I.

126. CIOMS Guidelines, *supra* note 118, at Background.

guidelines were produced.<sup>127</sup> The final redrafting committee included experts in ethics and research from every continent.<sup>128</sup> The 2002 Guidelines, like the *Belmont Report* in the United States, emphasize three overarching ethical principles: respect for persons,<sup>129</sup> beneficence,<sup>130</sup> and justice.<sup>131</sup> Unlike the Declaration of Helsinki, which includes broad, generalized principles, the 2002 Guidelines include extensive commentary designed to highlight the specific issues that have been discussed in academia regarding each guideline.

The 2002 Guidelines include twenty-one ethics guidelines for biomedical research at the international level.<sup>132</sup> Unlike the primacy of informed consent in the Code, the primary tenet of the 2002 Guidelines aligns the guidelines with the Declaration by requiring a showing of ethical and scientific justification for all research.<sup>133</sup> Guidelines on informed consent are numerous and detailed, but do not begin until Guideline 4.<sup>134</sup> Guidelines 2 and 3 relate to ethical review of research and will be discussed in further detail in Part V of this Note. The 2002 Guidelines

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127. *Id.*

128. *Id.*

129. Respect for persons includes respect for individual autonomy in making personal choices, as well as protection of persons with impaired or diminished autonomy. *Id.* at General Ethical Principles.

130. Beneficence is the "ethical obligation to maximize benefits and to minimize harms." *Id.*

131. Justice primarily refers of "distributive justice," which requires equitable distribution of burdens and benefits. *Id.*

132. *Id.* at Guidelines.

133. *Id.* Guideline 1 specifies:

The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's [sic] health. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risk without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

*Id.*

134. *Id.* Informed consent is at issue in Guidelines 4–6; consent issues with those unable to give full, informed consent are covered in Guidelines 9, 14 (children), and 15 (mental/behavioral disorders). *Id.*



also include specific provisions for dealing with vulnerable populations<sup>135</sup> and a controversial “choice of control” guideline.<sup>136</sup> The specific focus of the 2002 Guidelines on medical research conducted at the international level makes this document particularly valuable to investigators, sponsors, and host countries wishing to ensure the ethical soundness of their research programs.

*b. International Conference on Harmonization's Good Clinical Practices*

The substantial increase in regulations and guidelines directed at clinical research during the 1960s and 1970s coincided with expansion of the pharmaceutical industry into the global marketplace.<sup>137</sup> Despite common regulatory goals of assuring quality, safety and efficacy of new drugs, the specific technical

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135. *Id.* Vulnerable populations generally include prisoners, minorities, the mentally ill, the hopelessly ill, poor people and children. ADIL E. SHAMOO & DAVID B. RESNIK, RESPONSIBLE CONDUCT OF RESEARCH 184 (2003).

136. *Id.* at Guidelines. “Choice of control” generally refers to the type of treatment that a member of the control group in an experiment will receive. *See, e.g.,* Timothy S. Jost, *The Globalization of Health Law: The Case of Permissibility of Placebo-based Research*, 26 AM. J.L. & MED. 175 (2000). Considerable debate in bioethical circles is currently focused on the use of placebo-control studies. *Id.* A placebo is generally an inert substance given to a research participant in lieu of the treatment being received by the non-control group. *Id.* at 176. The debate around the use of placebo-control studies is particularly vociferous in research experiments that test drugs or procedures responsive to harms that already have alternative methods of treatment. *Id.* at 177. The question oft being: is it ethical to deny a known, proven treatment to any participant, even if that treatment would be unavailable to the participant outside of the research experiment? *See, e.g.,* Finkenbinder, *supra* note 95.

137. *See* ICH GLOBAL COOPERATION GROUP, INFORMATION BROCHURE 3–4 (2001) [hereinafter ICH INFORMATION BROCHURE], available at [http://www.ich.org/MediaServer.jserv?@\\_ID=410&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=410&@_MODE=GLB) (last visited Jan. 31, 2005). In its 2004 annual report, PhRMA, the largest U.S. association of pharmaceutical companies involved in research and development, stated that its members' research and development expenditures abroad increased by fifty times in the last thirty years. PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, PHARMACEUTICAL INDUSTRY PROFILE 2004, at 39 (2004) [hereinafter PhRMA 2004 PROFILE], available at <http://www.phrma.org/publications/publications//2004-03-31.937.pdf> (last visited Jan. 31, 2005). Additionally, the increase in research and development spending abroad out-paced domestic spending by more than 1000% over the same period. *Id.*

requirements that a drug needed to meet prior to approval for sale to the public varied substantially between countries.<sup>138</sup> As a result, the pharmaceutical industry was required to repeat time-consuming and expensive clinical trials<sup>139</sup> in each country in which they wanted to sell their drugs.<sup>140</sup> As a response to the growing globalization of the pharmaceutical industry and the regulatory burdens that new drugs faced when introduced to various countries' markets, many began to call for international harmonization of regulatory requirements.<sup>141</sup>

The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established in 1990.<sup>142</sup> The ICH is a joint initiative by regulators and industry in the three nations that

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138. ICH INFORMATION BROCHURE, *supra* note 137, at 4.

139. For example, in the United States, a new drug compound generally takes over ten years to proceed from the preclinical stage to approval for marketing at a cost of approximately \$800 million. *See, e.g., No New Drugs*, WALL ST. J., July 21, 2003, at A10; PhRMA 2004 PROFILE, *supra* note 137, at 2 (average new drug takes ten to fifteen years to get to market and costs approximately \$800 million to develop).

140. ICH INFORMATION BROCHURE, *supra* note 137, at 4. Repetition of clinical trials was burdening pharmaceutical companies' research & development budgets, impacting the overall cost of health care, and creating substantial delay in bringing safe and efficacious new treatments to patients. *Id.*

141. Official Website for the International Conference on Harmonization, History and Future of ICH, at [http://www.ich.org/UrlGrpServer.jsr?@\\_ID=276&@\\_TEMPLATE=254](http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254) (last visited Jan. 28, 2005). Initial harmonization of regulatory requirements was done by the European Community (now the European Union) in the 1980s. ICH INFORMATION BROCHURE, *supra* note 137, at 4. *See also* David Vogel, *The Globalization of Pharmaceutical Regulation*, 11 GOVERNANCE 1, 3–5 (1998). The desire to harmonize was expressed in diplomatic discussions between Europe, Japan and the United States during the same period. ICH INFORMATION BROCHURE, *supra* note 137, at 4. However, specific plans for action were not initiated until the 1989 WHO Conference on Drug Regulatory Authorities in Paris. *Id.* The planning at the WHO conference led to discussions between the authorities and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), which later hosted the first ICH meeting. *Id.*

142. ICH Steering Committee, Statement by the ICH Steering Committee on the Occasion of the Fourth International Conference on Harmonization (July 16–18, 1997), available at [http://www.ich.org/MediaServer.jsr?@\\_ID=348&@\\_MODE=GLB](http://www.ich.org/MediaServer.jsr?@_ID=348&@_MODE=GLB). A similar harmonization organization has been formed for the medical device sector, called the Global Harmonization Task Force, but this project is less formalized and is in an earlier stage of development than the ICH. D. B. Jefferys, *The Regulation of Medical Devices and the Role of the Medical Devices Agency*, 52 BRIT. J. CLIN. PHARMACOLOGY 229, 233–34 (2001).

dominate the development of new pharmaceutical products: the United States, Japan and the European Union.<sup>143</sup> The primary objective of the ICH is to:

[I]ncrease international harmonization of technical requirements to ensure that safe, effective and high quality medicines are developed and registered in the most efficient and cost-effective manner ... [in order to] promote public health, prevent unnecessary duplication of clinical trials in humans, and minimize the use of animal testing without compromising safety and effectiveness.<sup>144</sup>

To further this objective, harmonization projects have focused on four categories: Safety,<sup>145</sup> Quality,<sup>146</sup> Efficacy,<sup>147</sup> and a Multidisciplinary category for topics that do not fit nicely in the other categories.<sup>148</sup> One of the most widely-recognized products of the ICH, published in 1996, is the ICH Good Clinical Practices guidelines (GCP) for conducting clinical research.<sup>149</sup>

Unlike the previous guidelines, the ICH GCP is not focused solely upon ethical considerations in clinical research. Rather, the GCP is a technical document that includes guidance on the

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143. ICH INFORMATION BROCHURE, *supra* note 137, at 6. The ICH has six official parties, as well as observers whose participation is intended to act as a link to non-ICH nations. *Id.* The regulatory agencies involved in the ICH include the European Commission (European Union), the Ministry of Health, Labor and Welfare (Japan) and the FDA (United States). *Id.* at 6–7. Industry representation is provided by the European Federation of Pharmaceutical Industries and Associations, Japan Pharmaceutical Manufacturers Association, and PhRMA. *Id.* at 6–8. The observers to the ICH are Canada (represented by Health Canada), the European Free Trade Area (represented by Swissmedic Switzerland) and the World Health Organization. *Id.* at 8. Additionally, the ICH Secretariat is run by the IFPMA. *Id.* The IFPMA represents prescription drug manufacturers and the research-based pharmaceutical industry in fifty-six countries. Official Website for the International Conference on Harmonization, Structure of the ICH, at [http://www.ich.org/UrlGrpServer.jsr?@\\_ID=276&@\\_TEMPLATE=254](http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254) (last visited Jan. 22, 2005).

144. ICH GLOBAL COOPERATION GROUP, QUESTIONS & ANSWERS ABOUT ICH 5 (2000), available at [http://www.ich.org/MediaServer.jsr?@\\_ID=406&@\\_MODE=GLB](http://www.ich.org/MediaServer.jsr?@_ID=406&@_MODE=GLB) (last visited Jan. 22, 2005).

145. Safety topics are concerned with conduct and practice in pre-clinical research studies. *Id.* at 7.

146. Quality topics relate to chemistry, product controls and product manufacturing. *Id.*

147. Efficacy topics cover the conduct and reporting of clinical trials. *Id.*

148. *Id.*

149. See generally ICH GCP, *supra* note 30.

development of a research protocol, scientific considerations and documentary requirements, as well as ethical considerations in the testing of new pharmaceutical products.<sup>150</sup> Though the ICH focuses upon issues pertaining to pharmaceutical products, the GCP can be applied to all clinical investigations that use human subjects.<sup>151</sup> The GCP provides thirteen principles intended to ensure the safety of participants and production of accurate data from clinical trials.<sup>152</sup> The first GCP principle states that “[c]linical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the GCP and the applicable regulatory requirement(s).”<sup>153</sup> In particular, ethical review by an independent review committee<sup>154</sup> and informed consent by participants are emphasized.<sup>155</sup> The influence of the ICH GCP on regulations affecting clinical trials has been substantial in many nations, including the three ICH countries and many non-ICH countries.<sup>156</sup> As such, an ever-increasing number of clinical trials are being conducted under the guidance of the GCP.<sup>157</sup>

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150. *See id.* at 1 (“GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.”).

151. *Id.*

152. *Id.* at 8–9.

153. *Id.* at 8. There is no mention in the GCP of the version of the Declaration of Helsinki referred to in the Principles section; however, the publication date of the GCP, 1996, suggests that the GCP was influenced by the 1989 version of the Declaration.

154. The GCP, like the Declaration of Helsinki, states that all clinical trials must be supervised by an Institutional Review Board or and Independent Ethics Committee. *Id.* at 9. The specific requirements for review are very similar to the regulatory requirements of the Common Rule and the FDA. *See id.* at 10–13; *infra* Part III. A. 1. & 2. *See also* GLOBALIZATION OF CLINICAL TRIALS, *supra* note 34, at 3 (“[ICH GCP] guidelines are very similar to FDA regulations.”).

155. ICH GCP, *supra* note 30, at 17–21.

156. *See, e.g.*, GLOBALIZATION OF CLINICAL TRIALS, *supra* note 34, at 5 (“[M]any countries have adopted the Good Clinical Practice guidelines from the International Conference on Harmonization as their regulatory standard.”); Ministry of Health, Malaysian Guidelines for Good Clinical Practices iii (1999) (Malaysia’s Ministry of Health adopted the basic principles of the ICH GCP, with some minor modifications for local requirements), *available at* [http://www.vadscorner.com/Malaysian\\_gcp.PDF](http://www.vadscorner.com/Malaysian_gcp.PDF) (last visited Feb. 1, 2005).

157. GLOBALIZATION OF CLINICAL TRIALS, *supra* note 34, at 3.

## III. ETHICAL REVIEW OF PROPOSED HUMAN-SUBJECT RESEARCH

As one can see from the previous section, there is no shortage of ethical guides for researchers to choose from when conducting clinical trials. Yet, who is responsible for ensuring that ethical guidelines are followed? The answer to this question is not as simple or straightforward as many researchers, sponsors, and participants would hope. Rather, responsibility for ensuring ethical behavior in research projects varies depending on several variables, including: who has initiated the research project,<sup>158</sup> how the project is funded,<sup>159</sup> and the location where the research is going to take place.<sup>160</sup>

Society's extensive use of research places duties of public responsibility and accountability on researchers.<sup>161</sup> In designing a protocol, the individual researcher has initial responsibility for assuring that the project will be ethical.<sup>162</sup> The next step in the

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158. See discussion *infra* Parts III.A.–B. Research initiated by a U.S. pharmaceutical company will be guided by FDA regulations if the product is going to be marketed to the public. See *infra* Part III.A.2. Therefore, an IRB would be responsible for assuring ethical guidelines were followed. *Id.* However, if a research protocol was initiated by an individual researcher in the United States, who was not affiliated with a research institution, then U.S. regulations would not apply and the individual researcher would be the only entity responsible for assuring ethical conduct. See discussion *infra* Part III.A.

159. Projects funded in full or in part by the U.S. government are regulated by the Department of Health and Human Services, which requires research institutions to give assurances and ensure review by IRBs. See *infra* Part III.A.1. Projects funded entirely by private entities are not regulated unless the product will fall under FDA regulations. *Id.* at Part III.A.1.–2. Therefore, it would be up to the private sponsor to assure ethical behavior.

160. Most research projects in the United States are reviewed by IRBs, who ensure that ethical guidelines are followed. See *infra* Part III.A. However, if the project is conducted outside the United States, there is considerable variation in regulation of research and the identity of entities responsible for ethical conduct during clinical trials. See *infra* Part III.B.

161. Improper research has the potential to kill or harm participants during clinical trials as well as patients whose doctors use erroneous results in treatment; money or valuable resources can be wasted and improper or unreasonable laws and policies can result from unreliable or erroneous research results. SHAMOO & RESNIK, *supra* note 135, at 6. See also discussion of Dr. Bezwoda, *infra* Part I.

162. Standards of conduct binding all researchers emphasize honesty, integrity, trust, accountability, respect, confidentiality and fairness. SHAMOO & RESNIK, *supra* note 135, at 6. Adherence to these ethical tenets is useful in

chain of responsibility usually lies with a group of individuals who have volunteered to review other researchers' projects. These groups, called Research Ethics Committees (REC),<sup>163</sup> are often mandated by law.<sup>164</sup> RECs are generally responsible for reviewing and approving all proposed research involving human subjects prior to the initiation of any clinical trials.<sup>165</sup>

The primary purpose of RECs is to safeguard the rights and welfare of human research subjects.<sup>166</sup> Prior to RECs, the responsibility of balancing "society's interests in protecting the rights of subjects [with] developing knowledge that can benefit the subjects or society as a whole" fell solely to the researcher conducting an experiment.<sup>167</sup> RECs allow individuals independent of a research project to evaluate scientific and ethical validity.<sup>168</sup> Their main function is to determine whether research adequately addresses six general ethical norms: (1) good research design; (2) competent research investigators; (3) positive balance between potential harms and benefits; (4) informed consent; (5) equitable selection of research participants; (6) policy for dealing with research-related injuries.<sup>169</sup> Each country or institution differs on other specific qualities of RECs, such as membership and types of research reviewed.<sup>170</sup>

#### A. *Research Ethics Committees in the United States*

In the United States, ethical and scientific review of research proposals is conducted by a committee, called an Institutional Review Board, which is generally located at the site where the

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promoting the goals of research as well as effective collaboration between investigators. *Id.*

163. REC is a general term to describe these review committees; however, in Parts III.A–B., the descriptor "REC" will be reserved for review committees outside of the United States.

164. *See infra* Parts III.A.–B.

165. *See generally* NBAC INTERNATIONAL RESEARCH, *supra* note 16.

166. ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 326 (1988).

167. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, *REPORT AND RECOMMENDATIONS: ETHICAL GUIDELINES FOR THE DELIVERY OF HEALTH SERVICES BY DHEW 1–2* (1978).

168. *Id.*

169. LEVINE, *supra* note 166, at 19, 326.

170. *See infra* Part III.B.

research is to be conducted. IRBs were originally established by the National Research Act of 1974<sup>171</sup> as a response to several well-publicized cases of unethical medical interventions, including reports of research abuses at medical schools and hospitals.<sup>172</sup> There are approximately three to five thousand IRBs located in the United States.<sup>173</sup> IRBs are associated with hospitals, academic centers, managed care organizations, federal and state government agencies, and for-profit companies such as pharmaceutical companies and medical device manufacturers.<sup>174</sup>

### 1. U.S. Regulation—The Common Rule

The basic outline of IRBs is defined by U.S. Department of Health and Human Services (DHHS) Federal Policy for the Protection of Human Subjects,<sup>175</sup> also known as the “Common Rule.”<sup>176</sup> The Common Rule applies to all human-subject research conducted by researchers or institutions that have received funds from DHHS.<sup>177</sup> The Common Rule has three major components: assurances,<sup>178</sup> provisions on informed consent,<sup>179</sup>

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171. National Research Act, Pub. Law 93-348, § 474, 88 Stat. 342 (codified as amended in scattered sections of 42 U.S.C.). This is the same Act that established the National Commission that wrote the Belmont Report. *See infra* Part II.B.1.c.

172. OFFICE OF INSPECTOR GENERAL, DHHS, INSTITUTIONAL REVIEW BOARDS: PROMISING APPROACHES 3 (1998) (“[C]oncerns grew from stories of the abuse of subjects during the World War II trials at Nuremberg, the promotional distribution of thalidomide resulting in numerous children born with birth defects, the administration of cancer cells to chronically ill and senile patients at a hospital in New York, and others....”).

173. *Id.*

174. *Id.*

175. Protection of Human Subjects, 45 C.F.R. § 46 (2000).

176. Jennifer A. Henderson & John J. Smith, *Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls*, 57 FOOD & DRUG L.J. 445, 447 (2002) [hereinafter Henderson & Smith, *Federal & State Controls*].

177. 45 C.F.R. § 46.101. The Common Rule also applies to research conducted outside the United States by researchers or institutions receiving DHHS funding. *Id.*

178. 45 C.F.R. § 46.103. An “assurance” is documentation stating that an institution will comply with all DHHS regulations. *Id.* The assurance must include the ethical principles/code that the institution will use to evaluate research, the designation of one or more IRBs, identification of IRB members, and IRB procedures for initial and continuing review of research (including adverse events). *Id.*

and IRBs.<sup>180</sup> IRBs are required to have at least five members of varying professional backgrounds.<sup>181</sup> At least one member must come from a non-scientific profession, such as a lawyer, ethicist, or theologian.<sup>182</sup> Also, at least one member must have no direct affiliation with the institution at which the proposed research project will be completed.<sup>183</sup> Members are required to recuse themselves from the evaluation of any research in which they have a conflict of interest.<sup>184</sup> IRBs have the authority to “approve, require modifications in (to secure approval), or disapprove” research proposals.<sup>185</sup>

The Common Rule requires IRBs to evaluate proposed research based on criteria that directly relate to the provisions of the *Belmont Report*.<sup>186</sup> The Common Rule provides several criteria for approval of research proposals: (1) risks to participants are reasonably minimized; (2) risks are reasonable in relation to the expected benefits to the participant; (3) selection of participants will be equitable; (4) informed consent will be sought and documented from each participant; (5) provisions for data monitoring and protection of participants’ privacy.<sup>187</sup> Research proposals must demonstrate beneficence by demonstrating that risks to participants have been minimized.<sup>188</sup> Justice assessments require researchers to show that selection of participants

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179. 45 C.F.R. §§ 46.116–117.

180. 45 C.F.R. §§ 46.107–115.

181. 45 C.F.R. § 46.107(a). Additionally, “no IRB may consist entirely of men or women, or entirely of members of one profession.” 45 C.F.R. § 46.107(b).

182. 45 C.F.R. § 46.107(c). Other individuals may be invited to participate in the review process if the group determines that their professional expertise would be helpful in the evaluation process, however these individuals have no voting rights in the approval process. 45 C.F.R. § 46.107(f).

183. 45 C.F.R. § 46.107(d).

184. 45 C.F.R. § 46.107(e).

185. 45 C.F.R. § 46.109(a). An IRB should require documentation on informed consent or may waive consent in specific circumstances. 45 C.F.R. § 46.109(c). IRBs may require specific information to be added to consent forms in order to increase participant protection. 45 C.F.R. § 46.109(b).

186. *See* 45 C.F.R. § 46.111. The overriding principles of the Belmont Report—respect for persons, beneficence, and justice—are discussed *infra* Part II.B.1.

187. 45 C.F.R. § 47.111(a).

188. *See id.*



will be fair and equitable.<sup>189</sup> Respect for persons is applicable to informed consent requirements.<sup>190</sup>

## 2. U.S. Regulation—Food & Drug Administration

In order to sell a new drug or medical device in the U.S. market, a manufacturer must first obtain approval for the product from the FDA.<sup>191</sup> Any product manufacturer that applies for FDA approval must have its product tested in pre-clinical trials and have designed a research protocol, approved by an IRB, for testing the product in human subjects.<sup>192</sup> As a component of mandatory human-subject clinical trials, the FDA has its own regulations governing IRBs.<sup>193</sup> Though the scope of the FDA's regulatory impact extends to commercial, as well as federally-funded research projects, the main components of the Common Rule discussed above are mirrored in FDA regulations.<sup>194</sup>

### B. Research Ethics Committees in Other Countries

In other nations, the responsibility for conducting ethical and scientific review of research proposals is held by various entities. A country's Ministry of Health may be the primary reviewer of proposed research.<sup>195</sup> Some nations have national ethics boards, state or regional boards, or localized institutional review committees similar to those found in the United States.<sup>196</sup> Often there is a combination of review mechanisms, such as review by multiple institutional RECs or review by a

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189. *See id.*

190. *See id.*

191. *See, e.g.*, PETER B. HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW 513 (1991).

192. *See id.* There are some exceptions to the rule that a research project and application for FDA approval should happen simultaneously, such as when a manufacturer has data already available from a foreign clinical study. *See infra* Part V.B.

193. Institutional Review Board, 21 C.F.R. § 56.

194. MALONEY, *supra* note 108, at 59. *See also* Good Clinical Practice Program, *Comparison of FDA and HHS Human Subject Protection Regulations*, FDA Official website, at <http://www.fda.gov/oc/gcp/comparison.html> (last visited Feb. 16, 2005).

195. Nancy Kass & Adnan A. Hyder, *Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subject Regulations*, in 2 NBAC INTERNATIONAL RESEARCH, *supra* note 29, at B-49.

196. *Id.*

national review board and an institutional REC.<sup>197</sup> Some developing nations do not have regulations pertaining to human-subject research, and therefore responsibility for ethical review may lie with researchers or foreign sponsors.<sup>198</sup>

Different countries' ethical review procedures are helpful to understand the similarities and differences that exist between the United States and other nations. In 2001, the European Union (EU) adopted Directive 2001/20/EC (Directive),<sup>199</sup> modeled upon the ICH GCP and applicable to all member states, which directs harmonization in the EU of the technical requirements for the development of medicinal products.<sup>200</sup> According to the Directive, all member states are required to have RECs that have the same purpose and functions as U.S. IRBs.<sup>201</sup> RECs, similar to U.S. IRBs, are also mandated in Japan, Canada, Denmark, Finland, Iceland, Norway and Sweden.<sup>202</sup> In Central America, Costa Rica utilizes institutional review committees followed by review through the Ministry of Health.<sup>203</sup> A similar system of review exists in India.<sup>204</sup> Several Asian coun-

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197. See e.g., Hirtle, *supra* note 30, at 265–66.

198. See Kass & Hyder, *supra* note 195, at B-8.

199. Council Directive 2001/20/EC, 1990 O.J. (L 121) 34 (directing Member states in the implementation of good clinical practice in human-subject clinical trials).

200. See *id.* art. 1(2) (“Good clinical practice is a set of internationally recognized ethical and scientific quality requirements which must be observed for designing, conducting, recording or reporting clinical trials that involve the participation of human subjects.”).

201. See *id.* art. 6, 9(1). See also MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY, DESCRIPTION OF THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004, at 8–9, available at [http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/ctdregs\\_shortdesc.pdf](http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/ctdregs_shortdesc.pdf) (last visited Mar. 2, 2005).

202. WORLD HEALTH ORGANIZATION, GUIDELINES FOR GOOD CLINICAL PRACTICE (GCP) FOR TRIALS ON PHARMACEUTICAL PRODUCTS 5 (1995), available at <http://www.who.int/medicines/library/par/ggcp/GCPGuidePharmatrials.pdf> (last visited Feb. 8, 2005); Health Canada Official Website, Good Clinical Practice: Consolidated Guidelines, at <http://www.ncehr-cnerh.org/english/gcp> (last visited Feb. 8, 2005).

203. Jaime Daremblum, *Editorials: Drug Trials in the Third World*, WASH. POST, Jan. 5, 2001, at A20 (Mr. Daremblum is the Costa Rican Ambassador to the United States).

204. See, e.g., C.M. Gulhati, *Needed: Closer Scrutiny of Clinical Trials*, 12 IND. J. MED. ETHICS 4 (2004) (research protocols are reviewed by a hospital ethics committee and the Drugs Controller General, India (equivalent to Min-

tries have adopted REC regulations that are almost identical to the Common Rule; however, these RECs generally limit their review to research on pharmaceutical products.<sup>205</sup> In the vast majority of developing countries, RECs are non-existent or are mirrors of U.S. IRBs and rely heavily on U.S. regulations for procedural and substantive guidance.<sup>206</sup>

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istry of Health review)), *available at* <http://www.issuesinmedicalethics.org/121ed004.html> (last visited Feb. 9, 2005); Krishan Maggon, *Regulatory Reform and GCP Clinical Trials with New Drugs in India*, 1 CLIN. TRIALS 461, 462–63 (2004) (reviewing existing regulation of clinical trials and new reforms to allow trials following principles of the ICH GCP).

205. See, e.g., Ock-Joo Kim et al., *Current Status of the Institutional Review Boards in Korea: Constitution, Operation, and Policy for Protection of Human Research Participants*, 18 J. KOREAN MED. SCI. 3, 4 (2003). South Korean regulations are modeled upon the REC requirements outlined in the ICH GCP. *Id.* As noted in the discussion of the ICH GCP, *infra* Part II.B.2.ii., the guidelines for independent ethical review committees are almost identical to U.S. regulations. South Korea's regulations have only been fully in place since 2001, and therefore many Korean IRBs are still struggling with implementation. Kim, *supra*, at 4. Korean researchers and institutions have already complained of many of the issues that are prevalent with U.S. IRBs, including inconsistent regulation at the institutional level and insufficient national guidance on the actual functioning of RECs. *Id.* Since Korean IRBs have limited their review efforts to drug trials, other forms of human-subject research receive no review at all. *Id.* Singapore's IRBs are regulated by the "Singapore Guideline for Good Clinical Practice," which is based upon the ICH GCP. BIOETHICS ADVISORY COMMITTEE (SING.), RESEARCH INVOLVING HUMAN SUBJECTS: GUIDELINES FOR IRBS 1 (2004) [hereinafter SING. IRB GUIDELINES], *available at* <http://www.bioethics-singapore.org/resources/reports3.html> (last visited Feb. 6, 2005). In the last decade, Singapore has taken significant strides toward becoming a world-leader in biomedical research. *Is S'pore's Zeal Sending Wrong Signal?*, BUS. TIMES (Sing.), Apr. 8, 2003, *available at* 2003 WL 2352450. Singapore has extensive regulations pertaining to pharmaceutical clinical trials. SING. IRB GUIDELINES, *supra*, at 12. However, it has not developed regulations for human-subject clinical trials that do not involve the testing of new drugs. *Id.* Non-pharmaceutical research may receive ethical review *if* conducted in certain hospitals, as Singapore's Ministry of Health requires all government and restructured hospitals to have hospital ethics committees to review all types of human-subject research protocols conducted within the institution. *Id.* at 13. See also MINISTRY OF HEALTH SINGAPORE, NATIONAL MEDICAL ETHICS COMMITTEE: A REVIEW OF ACTIVITIES, 1994–1997 (1998); Andy Ho, *Medical Research—Who Watches Ethics Panels?*, STRAITS TIMES (Sing.), Apr. 16, 2003 (inspired by revelations that a prominent researcher, the head of the National Neuroscience Institute, had violated research ethics by failing to get IRB approval of his study and failing to obtain informed consent from research subjects), *available at* 2003 WL 16359464.

206. Kass & Hyder, *supra* note 195, at B-8.

Though the form of review may vary, consistent throughout the world is the fundamental purpose of RECs. They are the gatekeepers of research, charged with ensuring that clinical trials are scientifically and ethically valid. Research Ethics Committees and Institutional Review Boards are the protectors of the people, they are the entity primarily charged with assuring participant's health and well-being will be protected. Yet, RECs and IRBs are often asked to make their determinations without information that may be crucial to the validity of the research, as well as participants' safety. They are asked to make their determinations without knowing whether an investigator has a financial interest in the research she is conducting, an interest that may interfere with her obligations to participants.

#### IV. CONFLICTS OF INTEREST

A researcher's scientific and academic credentials are a common piece of information provided to RECs and IRBs evaluating a new research protocol.<sup>207</sup> Yet, are scientific and academic credentials sufficient information to evaluate researchers' ability and willingness to abide by ethical guidelines? What if a researcher has been influenced by private interests that may impact the project and put participants' safety and well-being at risk? Interests of a personal, financial, political, or other nature may conflict with professional, ethical, or legal obligations and duties.<sup>208</sup> Conflicts of interest (COIs) arise when a conflict occurs between interests and duties.<sup>209</sup> The first step in understanding the issues surrounding COIs is to properly define the phrase "conflict of interest."<sup>210</sup> An individual is described as having a conflict of interest when "he or she has personal, financial, or political interests that undermine his or her ability to meet or fulfill his or her primary professional, ethical, or legal obligations."<sup>211</sup> A medical researcher working with human

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207. See, e.g., ICH GCP, *supra* note 30, at 10 (§ 3.1.2 requires IRBs to obtain investigators' current curriculum vitae or other documentation evidencing qualifications).

208. SHAMOO & RESNIK, *supra* note 135, at 139.

209. *Id.*

210. *Id.* at 140.

211. *Id.* at 141, 145. This definition is limited to those conflicts which affect individuals, rather than organizations or institutions. *Id.*

subjects has a COI when she has any interests that undermine her duty to the health and safety of research subjects.<sup>212</sup> An “apparent COI” is described as a situation in which there is no actual interference with a researcher’s obligations, but the researcher holds some private interest that suggests that she *could* have a conflict.<sup>213</sup> The two primary concerns with COIs are that conflicts will: (1) interfere with an individual researcher’s judgment or reasoning<sup>214</sup> and/or; (2) unduly influence a researcher’s motivation and behavior during the experiment.<sup>215</sup>

Individual researchers are not the sole entities that may have interests that conflict. Institutions that conduct research also have conflicts of interest.<sup>216</sup> Institutions, including research institutions, government agencies, professional associations, and peer review journals often have collective duties to professionals, clients, students, patients, and the public.<sup>217</sup> An institution’s primary mission, be it research, education or public service, may be adversely affected by financial, political or other interests.<sup>218</sup> Conflicts of interest at the institutional level occur throughout the various components of an institutions’ management structure.<sup>219</sup> Institutional COIs and apparent COIs are a prominent discussion topic in academia due to the close collabo-

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212. See e.g., Daryl Pullman, *Conflicting Interests, Social Justice and Proxy Consent to Research*, 27 J. MED. & PHIL. 523 (2002).

213. SHAMOO & RESNIK, *supra* note 135, at 142.

214. *Id.* at 140. Interference with judgment or reasoning can result in an individual forming a particular bias. The individual researcher’s judgment is thereby skewed in a particular pattern or direction attributable to the conflicting interest. *Id.* at 141.

215. *Id.* at 141. Motivational and behavioral effects of conflicts of interest are distinct from circumstances in which an individual’s judgment is impaired by the conflicting interests. *Id.* In these situations, the individual acts against his or her duties because of the temptation to advance the conflicting interest to his or her personal advantage. *Id.*

216. See, e.g., Robert Gatter, *Human Subject Research and Conflicts of Interest: Walking the Talk of Trust in Human Subject Research: The Challenge of Regulating Financial Conflicts of Interest*, 52 EMORY L. J. 327, 344 (2003).

217. SHAMOO & RESNIK, *supra* note 135, at 145.

218. *Id.*

219. *Id.* Institutional COIs are created by the actions or behaviors of the institution, as well as by the judgment, decisions, and actions of the institution’s members—i.e., faculty, committees, advisory boards, deans, presidents and vice presidents. *Id.*

ration between private industry and research institutions.<sup>220</sup> Conflicts of interest can affect virtually any area of research; however, peer review (including IRBs) and clinical trials are particularly susceptible to conflicts.<sup>221</sup>

#### A. *Intrinsic Conflicts of Interest*

Some interests that conflict with an individual's primary duty to protect participants are intrinsic.<sup>222</sup> Intrinsic conflicts are ubiquitous in clinical research.<sup>223</sup> These interests form the primary motivation for conducting a research experiment in a variety of instances.<sup>224</sup> Intrinsic COIs are the self-interests of a researcher beyond the goals of advancing scientific knowledge or helping patients. The most common intrinsic COIs involve a researcher's desire for career advancement,<sup>225</sup> publication in prestigious journals<sup>226</sup> or to pioneer a successful technique.<sup>227</sup>

Certain intrinsic COIs are financial, though separate from types of individual financial gain that constitute financial COIs

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220. *Id.* at 172. See, e.g., Jennifer A. Henderson & John J. Smith, *Financial Conflict of Interest in Medical Research: Overview and Analysis of Institutional Controls*, 58 FOOD & DRUG L.J. 251, 251 (2003) [hereinafter Henderson & Smith, *Institutional Controls*].

221. SHAMOO & RESNIK, *supra* note 135, at 142.

222. Sharmon Sollitto et al., *Intrinsic Conflicts of Interest in Clinical Research: A Need for Disclosure*, 13 KENNEDY INST. ETHICS J. 83, 85 (2003).

223. *Id.* See also Norman G. Levinsky, *Nonfinancial Conflicts of Interest in Research*, 347 NEW ENG. J. MED. 759, 760 (2002).

224. Levinsky, *supra* note 223, at 760–61. The author points out that many of the self-interests that are defined as intrinsic COIs have been and will continue to be a legitimate part of research. *Id.*

225. The more research an investigator successfully completes and has had accepted by her peers, the greater the investigator's reputation and ability to direct her career as she wishes. See, e.g., Sollitto, *supra* note 222, at 85.

226. *Id.* ("The quality, placement, and number of the researcher's publications will affect national reputation and eligibility for academic advancement.")

227. *Id.* Other intrinsic COIs include "satisfaction of vindicating intellectual biases," the desire to win research prizes or for recognition and respect from peers, and certain types of financial incentives (other than those bring monetary benefit directly to the individual researcher). *Id.* at 85–86. The events surrounding HDC and Dr. Bezwoda are a perfect example of how this type of intrinsic conflict of interest may endanger participants' safety. See *infra* Part I.

(discussed *infra*).<sup>228</sup> The current funding scheme for medical research promotes intrinsic financial COIs, whether research is privately or publicly funded.<sup>229</sup> Continued funding of privately-sponsored research depends, in part, on researchers' and research institutions' ability to accrue and retain participants.<sup>230</sup> Publicly-sponsored research through government funding is also influenced by accrual and retention of participants. Renewal of existing government grants and the amount of funds allocated for a particular research project depends upon the ability to continue the research, by retaining previous participants, as well as enrollment of new participants.<sup>231</sup> These intrinsic financial incentives motivate researchers and institutions to enroll as many participants as possible for research projects, including some that may not be entirely appropriate for the study, thereby creating a potential conflict with patient safety concerns.<sup>232</sup> Despite their ubiquitous nature, intrinsic COIs have received little attention in academic discussions on medical ethics.<sup>233</sup> However, intrinsic COIs are as much a threat to patient safety as the financial COIs that have received substantial academic, media and regulatory attention.<sup>234</sup>

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228. Sollitto, *supra* note 222, at 86. Intrinsic financial interests generally are broader than individual financial interests as they involve issues of funding for current and future research—research that will in turn further reputation and publication. *Id.*

229. *Id.*

230. *Id.* Industry-sponsored research generally includes a contractually negotiated payment to investigators based upon the number of participants she signs up and who thereafter complete the treatment being researched. *Id.* These payments are intended to cover the investigator's research costs. *See, e.g.,* Karine Morin et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 J. AM. MED. ASS'N 78, 78–79 (2002). Therefore, these funds generally pay the researcher's and other research personnel's salaries and for facility overhead costs. Sollitto, *supra* note 222, at 86.

231. *Id.*

232. *Id.* A discussion of the risk to patients due to intrinsic COIs is included *supra* note 234.

233. *See, e.g.,* Levinsky, *supra* note 223.

234. *Id.* While much discussion of financial COIs followed revelation that a researcher and his research institution had significant financial COIs after a patient's death in 1999, intrinsic COIs were not part of the discourse following several other well-publicized deaths of healthy research participants where financial COIs did not exist. *Id.* However, it has been suggested that intrinsic COIs were influential in research that resulted in several deaths at leading research institutions. *See* Sollitto, *supra* note 222, at 86. A poignant ex-

*B. Financial Conflicts of Interest*

Financial COIs are a major issue discussed in reviews of the current medical research environment.<sup>235</sup> Research–industry collaborations often create concerns about conflicts of interest, bias, and impaired social responsibility in research findings.<sup>236</sup> In particular, commentators have noted that the private industry concepts of profit and competition are at odds with the scientific ideal of objectivity.<sup>237</sup> The substantial increase in funding of research by private industry has led to growing concern in recent years.<sup>238</sup> Since 1980,<sup>239</sup> private funding of research in all

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ample of ethics violations related to intrinsic COIs recently occurred in Singapore. *Is Spore's Zeal Sending Wrong Signal?*, *supra* note 205. In April 2003, the director of Singapore's National Neuroscience Institute was fired following revelations that he had conducted experiments on Parkinson's Disease patients without their consent and without submitting his research to ethical review. *Id.* The press pointed out that Singapore has openly campaigned for bring medical researchers to the country using various non-financial incentives. *Id.* An intrinsic financial COI existed as well, in the form of a ten million dollar government grant provided to the researcher's institution for his study. Zuraidah Ibrahim, *Medical Ethics? It's Something Money Can't Buy*, STRAITS TIMES (Sing.), Apr. 12, 2003, available at 2003 WL 16359084. See also, *Move to Plug Loopholes in Medical Research*, STRAITS TIMES (Sing.), Apr. 9, 2003, available at 2003 WL 16358811.

235. See, e.g., Henderson & Smith, *Institutional Controls*, *supra* note 220, at 251; Marci Angell, *Is Academic Medicine for Sale?*, 342 NEW ENG. J. MED. 1516, 1517 (2000) (“[C]lose and remunerative collaboration with a company naturally creates goodwill on the part of researchers and the hope that the largess will continue. This attitude can subtly influence scientific judgment in ways that may be difficult to discern.”).

236. SHAMOO & RESNIK, *supra* note 135, at 7. See also Sameer S. Chopra, *Industry Funding of Clinical Trials: Benefit or Bias?*, 290 JAMA 113, 113 (2003) (“Corporate financing of clinical research, which often includes incentives for academic investigators, may also create conflicts of interest that can bias study results.”); Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 JAMA 454 (2003) (evidence from multiple academic studies shows that financial ties between industry, researchers and research institutions leads to pro-industry research results).

237. See, e.g., SHAMOO & RESNIK, *supra* note 135, at 7; Chopra, *supra* note 236, at 113.

238. SHAMOO & RESNIK, *supra* note 135.

239. 1980 is particularly significant to reviews of private industry funding of research because this was the year the Bayh-Dole Act (35 U.S.C. § 200 et seq.) was passed. Henderson & Smith, *Federal & State Controls*, *supra* note 176, at 446. The Bayh-Dole Act changed intellectual property regulation of federally-funded research projects. The Act conferred ownership of intellectual prop-



scientific arenas increased four hundred percent.<sup>240</sup> Private industry funding of medical research grew at an exponentially greater rate, increasing by over thirty-three times (3300%) from 1980 to 2002.<sup>241</sup> A substantial portion of this increase in research expenditures has occurred in the last several years.<sup>242</sup> In 2005, the total U.S. expenditure on biomedical research is estimated to top \$100 billion.<sup>243</sup>

Financial COIs affect individual researchers as well as the institutions in which research is performed. For the individual researcher, financial COIs and apparent COIs occur when the researcher has a financial relationship with a research sponsor or with the manufacturer of the medical technology being studied.<sup>244</sup> Financial relationships may include ownership of company stock or stock options, unusually high consulting fees and speaking fees paid by manufacturers, or fees paid to community physicians for each patient they refer to participate in a company's clinical trials.<sup>245</sup> Institutional COIs include many of the same financial relationships that occur with individual re-

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erty to the entities that performed research, rather than the federal government. *Id.* As a result, the Act allowed universities, nonprofit corporations, and other businesses to commercialize federally-funded inventions and new technologies by giving these entities the power to patent their work. *Id.*

240. SHAMOO & RESNIK, *supra* note 135, at 7.

241. U.S. private-industry allocation for medical research in 1980 was approximately \$1.5 billion. Henderson & Smith, *Federal & State Controls*, *supra* note 176, at 446. In 2002, private-industry funding of medical research and development activities reached almost \$50 billion. RESEARCH!AMERICA, 2002 INVESTMENT IN U.S. HEALTH RESEARCH (2004), at <http://www.researchamerica.org/publications/appropriations/healthdollars2002.pdf> (last visited Feb. 8, 2005).

242. See e.g., EVA OHLIN, THE STRUCTURE AND FINANCING OF MEDICAL RESEARCH IN THE UNITED STATES 7 (2004) (The National Institute of Health, the federal government's major funding agency for medical research, has more than doubled its budget since 1998), available at [http://www.itps.se/pdf/A2004\\_006.pdf](http://www.itps.se/pdf/A2004_006.pdf) (last visited Feb. 2, 2005); PhRMA 2004 PROFILE, *supra* note 137, at 39 (PhRMA members research and development expenditures have double since 1996).

243. See OHLIN, *supra* note 242, at 7.

244. Gatter, *supra* note 216, at 340–48.

245. *Id.* at 340. Community physicians and physician-researchers are often paid between several hundred and several thousand dollars for every patient they enroll in an industry-sponsored clinical trial. Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at 11.

searchers.<sup>246</sup> Real and apparent financial COIs at the institutional level occur when the institution has a financial tie to a private industry research sponsor through ownership of stocks, industry sponsor fees paid to high-ranking individuals<sup>247</sup> within an institution for patient referrals, and through corporate sponsorship of research.<sup>248</sup> The issues associated with institutional COIs are particularly significant because most regulatory schemes make research institutions the primary protectors of research participants.<sup>249</sup> Regardless of whether the researcher or institution holds a conflicting interest, the risk that the conflict will interfere with the project and endanger participants is of fundamental concern.

#### V. REGULATORY REFORM: RESEARCH ETHICS COMMITTEES AND CONFLICT OF INTEREST POLICY

In the expanding global arena of medical research, the influence of U.S. regulations is considerable. Efforts to harmonize pharmaceutical regulations have resulted in substantial similarity between U.S. drug regulations and the corresponding regulations in many developed and developing nations.<sup>250</sup> Additionally, many clinical trials outside the United States, particularly those in developing nations, are financed by the U.S. government or by corporations that wish to market their product in the United States.<sup>251</sup> Consequently, these trials are required to comply with U.S. regulations.<sup>252</sup> As well, many developing countries conducting clinical trials do not have their own independ-

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246. Gatter, *supra* note 216, at 340–48.

247. The COIs of high ranking individuals within an institution are synonymous with institutional COIs because these individuals are the controlling body that guide the institution's actions and behavior. *See, e.g.,* SHAMOO & RESNIK, *supra* note 135, at 145.

248. Gatter, *supra* note 216, at 342–47.

249. *Id.* at 348.

250. *See infra* Part III.B.

251. Adnan A. Hyder et al., *Ethical Review of Health Research: A Perspective From Developing Country Researchers*, 30 J. MED. ETHICS 68, 70 (2004) (study of researchers in developing nations reported that almost half of all the research projects in those countries were funded by U.S. sources); PhRMA 2004 PROFILE, *supra* note 137, at 39.

252. *See infra* Part III.

ently-created regulations.<sup>253</sup> Rather, these countries use U.S. regulations as the guide for their medical research programs.<sup>254</sup>

This increasingly global reach of U.S. regulations on human subject research necessarily extends the problems, as well as the benefits, associated with those regulations. One continuing problem is the U.S. government's failure to give adequate regulatory guidance to RECs, researchers and research institutions on management of COIs. RECs are charged with protecting the health and safety of research participants.<sup>255</sup> They are the ethical "watchdogs" of biomedical research.<sup>256</sup> COIs promote bias that has the potential to impact participants' health and safety.<sup>257</sup> Yet, this important piece of information—whether a researcher has a COI—is often unavailable to the REC charged with evaluating a research project.<sup>258</sup> As the influence of U.S. regulations expands, the failure to adequately deal with COIs, "one of the most contentious issues in medicine today," broadens to become an international issue.<sup>259</sup> Now, deficiencies in

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253. See Kass & Hyder, *supra* note 195, at B-8 (study of U.S. and international researchers showed that the vast majority believed that developing country investigators "sometimes or always relied on U.S. human subject regulations for guidance"); Hyder, *supra* note 251, at 70 (study showed that more than two thirds of researchers in developing nations stated that they had relied upon U.S. ethics regulations for guidance).

254. Kass & Hyder, *supra* note 195, at B-8. Nations may also choose to adopt the GCP produced by the ICH (or the similar version published by the World Health Organization). See *infra* Part II.B.2. However, adoption of the GCP has a similar effect, creating a regulatory system that is almost identical to U.S. regulations. See GLOBALIZATION OF CLINICAL TRIALS, *supra* note 34, at 3.

255. See *infra* Part III.

256. See, e.g., Jennifer L. Gold, *Watching the Watchdogs: Negligence, Liability, and Research Ethics Boards*, 11 HEALTH L.J. 153 (2003) (discussing potential liability of IRBs for failure to take adequate precautions in protecting research participants health and well-being); Ho, *supra* note 205.

257. See *infra* Part IV. See also Jerome P. Kassirer, *Financial Conflicts of Interest: An Unresolved Ethical Frontier*, 27 AM. L.J. & MED. 149, 153 (2001).

258. See, e.g., Elaine Larson et al., *A Survey of IRB Process in 68 U.S. Hospitals*, J. NURS. SCHOLARSHIP 260, 261 (2004) (noting that only 10.3% of the hospital IRBs surveyed required a conflict of interest statement for a new research protocol); S. Van McCrary et al., *A National Survey of Policies on Disclosure of Conflicts of Interest in Biomedical Research*, 343 NEW ENG. J. MED. 1621, 1623 (2000) (survey of 235 medical schools and research institutions showed that only three institutions required disclosure of COIs to IRBs).

259. Kassirer, *supra* note 257, at 149.

U.S. policy on COIs are potentially injurious to research participants within *and* without the borders of the United States. The following sections discuss two regulatory reforms that are needed to allow RECs' review functions to properly align with their protective purpose.<sup>260</sup>

#### A. *Conflict of Interest Regulation in the United States*

Conflicts of interest<sup>261</sup> in medical research are regulated at three separate levels in the United States: federal, state and institutional.<sup>262</sup> These COI policies are directed solely at financial COIs. The federal level of COI controls consist of the Common Rule, Public Health Service (PHS) regulations, and FDA disclosure regulations.<sup>263</sup> State control over regulation of COIs in medical research is not statutory, but emanates primarily from state court decisions.<sup>264</sup> The vast majority of regulation of COIs occurs at the institutional level.<sup>265</sup> Based upon the mini-

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260. Admittedly, there are many more issues that require consideration when discussing realignment of RECs function and purpose; however, this discussion will be limited solely to the issue of COIs. For a few examples of IRB reform proposals, see, e.g., Michaele C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 NEW ENG. J. MED. 1405 (2002); Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANNALS INTERNAL MED. 282 (2004); Slater, *supra* note 14, at 1402.

261. The term COI in Part V. refers only to financial COIs. Intrinsic COIs would be almost impossible to regulate, as they are very difficult to identify and are ubiquitous in clinical research, and are therefore outside the scope of this discussion. See *infra* Part IV.A.

262. See, e.g., Henderson & Smith, *Federal & State Controls*, *supra* note 176 (providing overview of federal and state controls of medical research); Henderson & Smith, *Institutional Controls*, *supra* note 220 (providing overview of institutional controls of medical research).

263. 42 C.F.R. § 50.604 (2005) (PHS regulation on institutional responsibility for investigator COIs); 21 C.F.R. § 54 (2004) (FDA regulations regarding financial disclosure by investigators). See also Henderson & Smith, *Federal & State Controls*, *supra* note 176, at 447.

264. Henderson & Smith, *Federal & State Controls*, *supra* note 176, at 453–54 (describing how the California Supreme Court decision in *Moore v. Regents of University of California*, a decision based on lack of valid informed consent, also dealt with issues of conflict of interest at the institutional level). See *Moore v. Regents of Univ. of Cal.*, 793 P.2d 479 (Cal. 1990).

265. Federal regulations delegate the responsibility of creating COI policies to individual institutions. See 42 C.F.R. § 50.604; OFFICE FOR HUMAN RESEARCH PROTECTION, DEP'T OF HEALTH AND HUMAN SERVICES, FINANCIAL

mal guidance provided by federal regulations, each individual institution creates its own COI policy—resulting in policies that vary greatly from one institution to another.<sup>266</sup> This section emphasizes federal COI regulation and the impact of federal regulations on institutional COI policies.

There are various federal regulations of financial COIs. The Public Health Service (PHS) and FDA have regulatory provisions for financial COIs.<sup>267</sup> However, neither agency's regulations mention the role and responsibilities of IRBs in disclosure policies or management policies for financial COIs.<sup>268</sup> Nor do the regulations make specific provisions for how research institutions should manage COIs—leaving this component to the discretion of the institution.<sup>269</sup> Notably, the Common Rule, which represents the core of federal protections of human research subjects, lacks provisions for identification and management of institutional or investigator COIs entirely.<sup>270</sup>

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RELATIONSHIPS AND INTERESTS IN RESEARCH INVOLVING HUMAN SUBJECTS: GUIDANCE FOR HUMAN SUBJECT PROTECTION (2004), 69 Fed. Reg. 26,393 (2004) [hereinafter OHRP Final Guide] (HHS Final Guidance Document discussing ways institutions may choose to deal with investigator COIs), *available at* <http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf> (last visited Feb. 14, 2005).

266. See Van McCrary, *supra* note 258, at 1621; Henderson & Smith, *Institutional Controls*, *supra* note 220, at 252.

267. 42 C.F.R. § 50.604 (2005) (PHS regulation on institutional responsibility for investigator COIs); 21 C.F.R. § 54 (2004) (FDA regulations regarding financial disclosure by investigators). PHS regulations were promulgated in 1995 and the FDA's regulations were promulgated in 1998. OFFICE FOR HUMAN RESEARCH PROTECTION, DEP'T OF HEALTH AND HUMAN SERVICES, FINANCIAL RELATIONSHIPS IN CLINICAL RESEARCH: ISSUES FOR INSTITUTIONS, CLINICAL INVESTIGATORS, AND IRBS TO CONSIDER WHEN DEALING WITH ISSUES OF FINANCIAL INTERESTS AND HUMAN SUBJECT PROTECTION 1 (2001) [hereinafter OHRP Interim Guide], *available at* [http://www.ccnmtl.columbia.edu/projects/rcr/rcr\\_conflicts/misc/Ref/OHRP\\_CoI.pdf](http://www.ccnmtl.columbia.edu/projects/rcr/rcr_conflicts/misc/Ref/OHRP_CoI.pdf) (last visited Feb. 2, 2005).

268. OHRP Interim Guide, *supra* note 267, at 1.

269. PHS regulations require institutions to report the existence of COIs and management plans for COIs; however, there is no requirement to report the specific details of the COIs or the management plan. Van McCrary, *supra* note 258, at 1624. FDA regulations require specific, detailed documentation of COIs and management plans, but do not specify any particular management protocols that are preferable or considered more trustworthy. *Id.*

270. Henderson & Smith, *Federal & State Controls*, *supra* note 176, at 448. The only Common Rule statutory provision for COIs is the restriction of IRB membership against any individual who has an interest in the research being reviewed by the IRB. 46 C.F.R. § 46.107(e). The Office for Human Research

The lack of specificity in federal regulations has had a significant impact upon the development of COI policies at the institutions where research is conducted. A national survey of research institutions came to the conclusion that the only universal feature to all COI policies was that they were totally discretionary.<sup>271</sup> Disclosure policies required that investigators disclose COIs to another member of the research institution; however, only one percent of institutions required disclosure to an IRB.<sup>272</sup> Management of disclosed COIs is even less consistent. Many institutions require additional project monitoring, request investigators withdraw from the project, or require investigators to divest their interests prior to continuance of the project when a COI exists.<sup>273</sup> However, none of the institutions required that COIs should be managed through disclosure to an IRB.<sup>274</sup>

Inconsistent COI policy at the institutional level reflects the lack of specificity at the federal level and makes the need for reform clear. Federal regulations need to specify exactly who must be informed of investigator COIs. So the question then becomes: who *needs* to know about investigator COIs? The FDA requires disclosure of COIs to the agency and to the sponsor of the research.<sup>275</sup> PHS regulations require that the agency<sup>276</sup> and

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Protections (OHRP), the main research oversight body of the DHHS, developed a set of draft interim provisions for identification and management of financial COIs in January 2001. See OHRP Interim Guide, *supra* note 267. In May 2004, the OHRP published the agency's Final Guidance Document. OHRP Final Guide, *supra* note 265. However, commentators have suggested that the final document "seem[s] to be more suggestions than hard and fast recommendation." Alicia Ault, *HHS Issues Rules on Financial Conflicts*, 363 LANCET 1709, 1709 (2004). No COI guidance statements have been codified to date.

271. Van McCrary, *supra* note 258, at 1622.

272. *Id.* at 1623. Additionally, only 8% required disclosure to the funding agency, 7% disclosed to journals publishing the research and 1%—3 of 250 institutions—required disclosure to participants. *Id.*

273. *Id.* Subsequent disclosure to the funding agency, modification of the research plan, and public disclosure of the COI are other common management techniques used by institutions. *Id.*

274. *Id.* None of the management policies required subsequent disclosure to research participants. *Id.*

275. 21 C.F.R. § 54.4.

276. In this situation, the agency would also be one of the sponsors, since PHS regulations only apply to research projects funded in full or in part by the agency. See *infra* Part III.A.

research institution are informed of investigators' COIs.<sup>277</sup> Federal agencies, sponsors and institutions are informed. What about the body that is charged by both of these agencies with ensuring that research is not initiated unless participants will be protected from undue risk? What about IRBs? No federal regulations specifically require that COIs be disclosed to a reviewing IRB. This failure needs to be remedied.

The purpose of ethical review is to "contribute to safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants."<sup>278</sup> While it is true that IRBs are heavily burdened by an ever-increasing load of research protocols to review, this does not mean that information on investigator COIs should be left out of the review process.<sup>279</sup> A primary function of the IRB is to analyze the protocol and ensure that the risks to participants have been accounted for, acknowledged, and then balanced with the potential benefits.<sup>280</sup> COIs, no matter how unlikely they are to actually harm a participant, are a risk. As such, they need to be included in any risk/benefit analysis done by an IRB. Without knowledge of investigator COIs, an IRB may not only fail to fulfill one of its functions but may also fail in its primary purpose—ensuring that research participants health and well-being is protected. Additionally, without COI disclosure, IRBs are unaware of the potential need for increased and/or more extensive evaluation of the project after approval—again interfering with its ability to safeguard participants.

Federal regulatory agencies' failure to make it clear that IRBs need to be provided full documentation of COIs is unacceptable. Existing regulations merely give lip service to the import of COIs and their potential risk to participants. It is time for DHHS and its agencies to provide more definitive,

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277. 42 C.F.R. § 50.604

278. WORLD HEALTH ORGANIZATION, OPERATIONAL GUIDELINES FOR ETHICS COMMITTEES THAT REVIEW BIOMEDICAL RESEARCH 1 (2000) (Doc. # TDR/PRD/ETHICS/2000.1), available at <http://www.who.int/tdr/publications/publications/pdf/ethics.pdf> (last visited Feb. 27, 2005).

279. See, e.g., Lars Noah, *Deputizing Institutional Review Boards to Police (Audit?) Biomedical Research*, 25 J. LEGAL MED. 267, 293 (2004) ("In the area of human research subject protection, better guidance from the FDA, HHS, and NIH would have the dual benefit of minimizing inconsistency and relieving already overburdened IRBs.").

280. See *infra* Part III.A.

harmonized regulations for COIs.<sup>281</sup> The best way to begin this reform process is to require that IRBs are *always* provided COI disclosure statements and management plans from investigators.

### *B. Regulations Affecting Foreign Clinical Studies*

Changes to U.S. regulations, as described above, will help to re-align the purpose and function of research ethics committees in the United States and in other nations that host research projects funded in full or in part by the U.S. government.<sup>282</sup> However, the scope of U.S. regulatory influence outside the United States extends beyond projects that receive funding from the U.S. government. The U.S. market is one of the world's largest consumers of pharmaceuticals and medical devices.<sup>283</sup> As such, manufacturers of these products often wish to have their products approved for marketing in the United States.<sup>284</sup> Fortunately for international manufacturers, the FDA allows data from foreign clinical studies to be used in the approval process for drugs and medical devices.<sup>285</sup> Most manufac-

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281. Even some agencies within the federal government have recognized that this is a serious flaw in existing human-subject research regulations. See GOVERNMENT ACCOUNTING OFFICE, BIOMEDICAL RESEARCH: HHS DIRECTION NEEDED TO ADDRESS FINANCIAL CONFLICTS OF INTEREST 22-25 (2001) (Report # GAO-02-89), available at <http://www.gao.gov/new.items/d0289.pdf> (last visited Feb. 15, 2005). However, action has yet to be taken.

282. As noted earlier, the Common Rule and PHS regulations only apply to research that is funded, at least in part, by the U.S. government. See *infra* Part III.A.

283. See, e.g., Press Release, IMS Health, IMS Reports 8 Percent Constant Dollar Growth in 2002 Audited Global Pharmaceutical Sales to \$400.6 Billion (Feb. 25, 2003), at [http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599\\_3665\\_41336931,00.html](http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_41336931,00.html). U.S. pharmaceutical sales represented 51% of global sales in 2002. *Id.* The second largest pharmaceutical market was the European Union, with 22% of global sales. *Id.*

284. Between 1998 and 2003, the FDA received over 12,000 IND applications. Center for Drug Evaluation and Research, *Original INDs Received Calendar Years 1986-2003*, FDA Official Website, at <http://www.fda.gov/cder/rdmt/Cyindrec.htm> (last visited Feb. 15, 2005).

285. 21 C.F.R. § 312.120 (2004) (drugs); 21 C.F.R. § 814.15 (2004) (medical devices). FDA policy associated with acceptance of foreign clinical data has evolved significantly over the last forty years. John Gorski, *An FDA-EEC Perspective on the International Acceptance of Foreign Clinical Data*, 21 Cal. W. INT'L L.J. 329, 333 (1991). The FDA allowed foreign clinical data to supplement domestic safety and efficacy findings beginning in 1962. *Id.* Foreign



turers file an Investigational New Drug (IND) application with the FDA prior to beginning clinical trials.<sup>286</sup> However, FDA regulations also allow manufacturers to support their market approval applications using data solely from previously conducted clinical trials located at foreign sites.<sup>287</sup>

In addition to several general technical requirements placed upon foreign clinical data, the FDA regulations include an ethics component.<sup>288</sup> Specifically, the FDA's foreign clinical studies regulations require collection of clinical data consistent with "ethical principles acceptable to the world community."<sup>289</sup> The regulations specify adherence to the 1989 Declaration of Helsinki<sup>290</sup> or "the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual."<sup>291</sup> Along with other documentary re-

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clinical data was not allowed as primary safety and efficacy data until 1975, but only for drugs that treated uncommon diseases, provided a major health gain, or had an exceptionally favorable benefit/risk ratio. *Id.* Starting in 1984, the FDA accepted foreign clinical data as primary evidence for all drugs seeking approval for marketing in the United States. *Id.* at 334.

286. An IND application based solely on foreign clinical data must meet the requirements of 21 C.F.R. § 314.106 (2004). Foreign clinical trials conducted under an IND must meet the same requirements as domestic clinical trials. *See* 21 C.F.R. § 312 (2004). According to the CDER, approximately 15% of trials submitted to the FDA with marketing applications were not conducted under an IND. Human Subject Protection: Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 69 Fed. Reg. 32467, 32471 (proposed June 10, 2004) (to be codified at 21 C.F.R. pt. 312).

287. 21 C.F.R. § 312.120; 21 C.F.R. § 814.15.

288. General technical components required by the FDA include: studies must be (1) well designed; (2) well conducted; and (3) performed by qualified investigators. 21 C.F.R. § 312.120(a). The data that is submitted to the FDA must include: (1) description of investigator's qualifications; (2) description of research facility; (3) summary of the protocol and the study's results; (4) full description of the substance and product used in the trials; and (5) information showing that the clinical trials were adequate and well controlled. 21 C.F.R. § 312.120(b).

289. 21 C.F.R. § 312.120(a). The medical device regulations use a slightly different wording, requiring that clinical data must be "valid." 21 C.F.R. § 814.15(b). With any application, foreign or domestic, if the FDA considers any data suspect, or believes it is unduly biased, the agency can reject the data outright. *See* Van McCrary, *supra* note 258, at 1624.

290. *See infra* Part II.

291. 21 C.F.R. § 312.120(c)(1). The regulations pertaining to premarket approval of medical devices states that an applicant must follow whichever

quirements, foreign investigators must submit attestations detailing how their research program complied with the 1989 Declaration<sup>292</sup> or the host country's ethical standards.<sup>293</sup>

While the Declaration of Helsinki provides major guidance for researchers, the FDA's insistence on usage of the 1989 Declaration results in an insufficient level of protection for research subjects. The 1989 Declaration has several significant deficiencies that reflect that this document is outdated. For example, the 1989 Declaration is not responsive to several of the largest issues confronting medical researchers today, including stem cell research and use of placebo-controls.<sup>294</sup> Additionally, while the 1989 Declaration provides that all research proposals must be reviewed by an REC, there is no mention of continuing review to ensure that ethical standard are being applied in practice as well as on paper.<sup>295</sup> Key to the discussion of COIs in biomedical research, the 1989 Declaration lacks any provisions for the disclosure or management of investigator COIs.<sup>296</sup>

Significantly, the FDA has recently proposed a major change in its foreign clinical studies regulations.<sup>297</sup> Acknowledging that standards for human subject protection have changed consid-

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standard "accords greater protection to the human subject." 21 C.F.R. § 814.15(b).

292. Even though 21 C.F.R. § 312.120 was adopted in 1991, the FDA has declined to revise the regulations to include the 1996 or the 2000 revisions of the Declaration of Helsinki. FDA GUIDANCE REPORT, *supra* note 100. In a 2001 published statement, the FDA stated that it was reviewing whether its regulations on foreign clinical studies needed revision to incorporate new or modified standards. *Id.* No action has been taken to date. *Id.*

293. If the research protocol followed the host country's ethical standards and regulations, the investigator must provide a written explanation of how the host country's standards are equivalent or superior to the 1989 Declaration. 21 C.F.R. § 312.120(c)(2).

294. *See generally* Forster, *supra* note 94. As an example of this assertion, one of the amendments to the 2000 Declaration was the addition of specific provisions on the use of placebos in medical research. *Id.* at 1452. An addendum on the same subject was added in 2002 in response to extensive discord in the ethics community over the use of placebos in developing countries. *Id.* Additionally, stem cell research would not accurately be regulated by the 1989 Declaration, as the 1989 Declaration only protects human subjects and not "human material." *Id.* at 1451.

295. *See* 1989 DECLARATION, *supra* note 87.

296. *Id.*

297. Human Subject Protection: Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 69 Fed. Reg. 32,467.

erably in the last decade, the agency has proposed removing the 1989 Declaration from its foreign clinical studies regulations.<sup>298</sup> In its stead, the FDA would require clinical trials to comply with the ICH GCP.<sup>299</sup> As a more detailed guidance for foreign investigators, the inclusion of the ICH GCP will certainly remove confusion about FDA documentation requirements and the specific responsibilities of various parties in research programs and marketing approval applications.<sup>300</sup> For the purposes of this Note, the question is whether the ICH GCP has provisions for COIs. Unfortunately, since the GCP mirrors U.S. human-subject research regulations, it also carries the same flaws discussed in the previous section. The ICH GCP requires documentation of financial arrangements among investigators, institutions and sponsors.<sup>301</sup> Yet, these documents are only required to be maintained by the sponsor and research institution.<sup>302</sup> As with the 1989 Declaration and U.S. regulations, the ICH GCP does not require that RECs are provided COI disclosure statements.<sup>303</sup>

Current international ethics guidelines reflect recognition for the need to include RECs in the management of COIs. In acknowledging that COIs have the potential to impact research participants' health and well-being, both the 2000 Declaration and the 2002 CIOMS Guidelines have made specific provisions that require RECs be provided information on investigators' COIs.<sup>304</sup> The revision of the Declaration of Helsinki in 2000 marked several major changes to the Declaration, including the

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298. *Id.* at 32,468. The FDA specifically stated that it felt the need to remove reference to the 1989 Declaration because modifications to the Declaration are outside of the agency's authority and "could be modified to contain provisions that are inconsistent with U.S. laws and regulations." *Id.*

299. *Id.* at 32,467.

300. *Id.* at 32,468. See also John Sweatman, *Good Clinical Practice: A Nuisance, a Help or a Necessity for Clinical Pharmacology?*, 55 BRIT. J. CLIN. PHARMACOLOGY 1, 2-4 (2003).

301. ICH GCP, *supra* note 30, at 51 (§ 8.2.4).

302. *Id.*

303. IRBs are required to be given documentation of payments or compensation given to research subjects, but the ICH GCP does not mention providing IRBs with documentation of investigator's financial interests with the project or its sponsors. *Id.* at 10 (§ 3.1.2).

304. Provisions on COIs in both of these documents are provided in the remainder of this section. See *supra* notes 303-305 (2000 Declaration), 306-308 (CIOMS Guidelines) and accompanying text.

adoption of three separate provisions that include requirements for disclosure of COIs.<sup>305</sup> Provision 13 of the 2000 Declaration includes specific provisions for the information that investigators are responsible for providing to RECs.<sup>306</sup> Under the 2000 Declaration, researchers are obligated to provide RECs with all information necessary for monitoring the project and submitting to the REC all “information regarding funding, sponsors, institutional affiliations, [and] other potential conflicts of interest.”<sup>307</sup> The 2002 CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* also ties RECs and disclosure of COIs.<sup>308</sup> The 2002 Guidelines’ recommendations on RECs<sup>309</sup> include commentary suggesting that RECs should be informed by investigators of any potential or apparent financial COIs.<sup>310</sup>

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305. 2000 DECLARATION, *supra* note 96. *See also* Forster, *supra* note 94, at 1449. Provisions 13, 22 and 27 include provisions for disclosing COIs. 2000 DECLARATION, *supra*. Provision 22 requires disclosure of possible COIs to research participants. *Id.* Provision 27 requires disclosure of COIs in publications of research materials and findings. *Id.*

306. *Id.* Unlike the 1989 Declaration, the 2000 Declaration requires all human-subject research be submitted to an independent ethical review committee. *Id.* Additionally, under the 2000 Declaration, RECs are specifically given the right to monitor ongoing research projects. *Id.*

307. *Id.*

308. CIOMS Guidelines, *supra* note 118.

309. CIOMS “Guideline 2: Ethical Review Committees” states:

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

*Id.*

310. *Id.* The CIOMS “Guideline 2: Ethical Review Committees” commentary states:

*Potential conflicts of interest related to project support.* Increasingly, biomedical studies receive funding from commercial firms. Such sponsors have good reasons to support research methods that are scientifically and ethically acceptable, but cases have arisen in which the conditions of funding could have introduced bias .... As persons

A link between RECs and disclosure and management of COIs is gaining acceptance as an international standard. It is no longer appropriate for U.S. regulators to hold foreign clinical studies to a standard recognized by the international bioethics community as insufficient for modern ethical problems. While the FDA's proposal to replace the 1989 Declaration with the ICH GCP will ameliorate several deficiencies within the existing foreign clinical studies regulations, it still requires further amendment. In order to provide appropriate protection for research participants, U.S. foreign clinical studies regulations should respond to the current needs of medical research and specifically require review of foreign clinical studies by an REC that has been provided documentation regarding investigators' COIs.

## VI. CONCLUSION

Intrinsic and financial conflicts of interest are a threat to the health and safety of research participants in the United States and abroad. Investment in clinical trials by industry and the federal government continues to increase in the U.S. and abroad, with industry financing now outpacing the U.S. government.<sup>311</sup> With this change in the support structure of clinical research, comes an increased likelihood that investigators will have financial conflicts with research sponsors that may impact the integrity of the project and the safety of participants. Stud-

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directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, to prepare manuscripts, or to publish them. Investigators must also disclose potential or apparent conflicts of interest on their part to the ethical review committee or to other institutional committees designed to evaluate and manage such conflicts. Ethical review committees should therefore ensure that these conditions are met.

*Id.* Researchers who participate in international clinical trials tend to believe that U.S. IRB review and application of U.S. regulatory requirements are often inappropriate outside the borders of the United States. Kass & Hyder, *supra* note 195, at B-64. Rather, these researchers suggest ethical review in the host country and that international guidelines should be the standard for evaluating projects; in particular, they suggest using the CIOMS guidelines for research in developing countries. *Id.*

311. See, e.g., PhRMA 2004 PROFILE, *supra* note 137, at 39; OHLIN, *supra* note 242, at 7.

ies have already shown that industry-funded clinical research is more likely to favor the sponsor than research conducted independent of industry funding.<sup>312</sup> Such trends support the assertion that COIs will only increase in the future. Yet, policies for the disclosure and management of COIs are inconsistent or non-existent in developed, as well as developing, nations. This failure to adequately provide guidance on investigator COIs shows a breakdown in the protection of citizenry that is the mandate of national and international health regulators.

RECs are the bodies that have been consistently charged with ensuring the protection of human subjects in medical research. It is only logical that they should have access to the same information that investigators, agencies, and institutions have regarding potential risks to research participants. Yet, they often lack any knowledge of investigators' financial interests that may cause bias or inappropriately influence decision-making. This failure is unacceptable, particularly since it is a failure easily remedied by simply adding regulations that mandate disclosure of COIs to IRBs. While there may be several other regulatory changes with greater potential to improve the system of human subject protection, this is one of the simplest. There is no excuse for the continuing lack of action by the federal government in this area.

Influence of U.S. regulations on medical research conducted throughout the world is substantial. With influence, comes responsibility. The fact that U.S. regulations propagate policies that are inconsistent with the goal of protecting the health and safety of research participants is unacceptable. The United States has a responsibility to conduct regulatory reform that

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312. Bekelman, *supra* note 236, at 454.

will more reasonably protect participants and support the purpose of ethical review.

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\* B.A., University of Washington (1994); M.Ed., University of Washington (1996); J.D., Brooklyn Law School (expected 2005). I dedicate this Note to my husband, Dr. Erik N. Kubiak, who inspired my interest in bioethics and has shown unending patience throughout my law school career. I wish to thank my friends and family for their continuing support of my life endeavors. I would also like to thank the staff of the *Brooklyn Journal of International Law* for their assistance and encouragement, and particularly Erin McMurray, Adrienne Oppenheim and Nicole Skalla for their support and patience as I struggled through the editing process.