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# COMMENTS

## HUMAN EXPERIMENTATION IN DEVELOPING COUNTRIES: IMPROVING INTERNATIONAL PRACTICES BY IDENTIFYING VULNERABLE POPULATIONS AND ALLOCATING FAIR BENEFITS

KRISTEN FARRELL\*

### INTRODUCTION

Developing countries often serve as desired locales for clinical research. The last decade witnessed a marked expansion in international health care research,<sup>1</sup> especially in clinical drug and vaccine trials funded by sponsors in wealthy countries and conducted in developing nations.<sup>2</sup> The target populations for clinical research in developing countries often have no access to basic health care, lack an understanding of the research, and are politically powerless.<sup>3</sup> Governments of host nations frequently view clinical research as a way to provide otherwise unaffordable medical care.<sup>4</sup> The sponsors of the clinical trials gravitate to developing countries because of lower costs, the prevalence of diseases, and seemingly limitless numbers of impoverished patients.<sup>5</sup> Of course, this potentially exploitative clinical research also serves a valuable purpose because it develops life-saving and life-improving medications. Moreover, this research may be the best source of health care available to certain vulnerable populations.

This Comment argues that a cohesive and effective international standard must be developed to protect and serve vulnerable populations in developing nations. An effective standard will recognize that potential benefits exist for drug companies and the people on whom they conduct experiments. On one side, governments and pharmaceutical companies stand to receive financial benefits and achieve medical progress. On the other side, developing countries may have

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1. James V. Lavery, *Putting International Research Ethics Guidelines to Work for the Benefit of Developing Countries*, 4 YALE J. HEALTH POL'Y L. & ETHICS 319, 320 (2004).

2. *Id.*

3. Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, *Fair Benefits for Research in Developing Countries*, 298 SCI. 2133 (2002) [hereinafter *Fair Benefits*].

4. Finnuala Kelleher, Note, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J.L. & SOC. PROBS. 67, 85 (2004). Many host countries lack any regulation on clinical trials. *Id.*

5. *Id.* at 67.

access to health care that would not otherwise be available to them. Part One examines the potential for exploitation by discussing Pfizer's experiments in Nigeria and vaccine tests conducted by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) in several African nations. Part Two explores the present standards governing human experimentation in an international context. Part Three analyzes these standards and identifies areas for improvement. Based on this analysis, Part Four recommends an international standard involving a heightened attention to informed consent, recognition of vulnerable populations, and a fair allocation of benefits.

#### I. THE POTENTIAL FOR EXPLOITATION OF VULNERABLE POPULATIONS

*Abdullahi v. Pfizer, Inc.*<sup>6</sup> illustrates the problems that arise when vulnerable populations suffer as a result of their participation in clinical research studies. This case involved clinical tests conducted by Pfizer, the world's largest pharmaceutical company.<sup>7</sup> In the process of developing Trovan, an antibiotic with the potential for producing \$1 billion a year in profits,<sup>8</sup> Pfizer seized an opportunity to test the drug in April 1996. That year, the Nigerian city of Kano suffered through epidemics of bacterial meningitis, measles, and cholera.<sup>9</sup> Six weeks after learning of the epidemics, a Pfizer medical team set up a treatment center at Kano's Infectious Disease Hospital.<sup>10</sup>

Prior to clinical testing at Kano, only one child had ever been treated with Trovan.<sup>11</sup> Animal testing of Trovan demonstrated that it might cause damaging side effects in children, such as joint disease, abnormal cartilage growth, and liver damage.<sup>12</sup> These troubling facts compound the apparent lack of consent on behalf of the research subjects. Although Pfizer sought permission from the parents of the children too young to provide consent, few parents read or spoke English.<sup>13</sup> Furthermore, plaintiffs alleged, Pfizer did not explain "that the proposed treatment

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6. 77 F. App'x 48, 51 (2d. Cir. 2003).

7. *PFIZER INC.: World's largest, research-based, pharmaceutical company created*, BIOTECH WEEK, May 14, 2003, at 94.

8. *Abdullahi v. Pfizer, Inc.*, No. 01 Civ. 8118, 2002 U.S. Dist. LEXIS 17436, at \*2-3 (S.D.N.Y. Sept. 16, 2002).

9. *Id.* at \*2.

10. *Id.* at \*2-3. Plaintiffs further alleged that "Pfizer's sole purpose for traveling to Kano was to expedite the FDA's approval of Trovan to treat pediatric victims." *Id.* at \*4.

11. *Id.*

12. *Id.* at \*2.

13. *Id.* at \*5.

was experimental, that [subjects] could refuse it, or that other organizations offered more conventional treatments at the same site free of charge.”<sup>14</sup>

Pfizer’s medical team left Kano after two weeks and never returned for any follow-up evaluations.<sup>15</sup> Several Nigerian minors and their guardians brought a class action suit against Pfizer,<sup>16</sup> in which they alleged that eleven children died and a number of others suffered from paralysis, deafness, and blindness from their treatment with Trovan.<sup>17</sup> They alleged violations of the law of nations under the Nuremberg Code (“Cod”), the Declaration of Helsinki (“Declaration”), the International Covenant on Civil and Political Rights (ICCPR), and customary international law.<sup>18</sup> Pfizer moved to dismiss the complaint for forum non conveniens and failure to state a claim.<sup>19</sup>

The U.S. district court granted Pfizer’s motion to dismiss, on the conditions that Pfizer consent to suit and accept process in any action the plaintiffs may file in Nigeria on the same claims.<sup>20</sup> On appeal to the U.S. District Court of Appeals for the Second Circuit, the plaintiffs argued that a parallel action in *Zango v. Pfizer* had already been filed and dismissed in Nigeria.<sup>21</sup> The plaintiffs also argued that in the notice for discontinuance, the Nigerian judge declined jurisdiction “for personal reasons.”<sup>22</sup> The Second Circuit subsequently vacated and remanded the district court’s decision for further proceedings to determine what precipitated the dismissal in *Zango*.<sup>23</sup>

Private pharmaceutical companies are not alone in using developing countries’ vulnerable populations for clinical trials. Between 1994 and 1997, the CDC and NIH conducted experiments on pregnant women infected with HIV in Thailand, the Dominican Republic, and several African nations.<sup>24</sup> These experiments were intended to create a more effective way of treating AIDS

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14. *Id.* at \*6. Humanitarian organizations such as Medecins Sans Frontieres (MSF), also known as Doctors Without Borders, also set up in Kano to treat the sick. *Id.* at \*3.

15. *Id.* at \*6.

16. *Id.* at \*1.

17. *Id.* at \*6.

18. *Id.* at \*1.

19. *Id.*

20. *Id.* at \*38. The other conditions for the dismissal were that Pfizer waive any statute of limitations defense, Pfizer make available for discovery and for trial—at its own expense—any documents or witnesses within its control that would be needed for a fair adjudication of the plaintiffs’ claims, and that Pfizer would not act to prevent plaintiffs from returning to the district court if the Federal High Court in Nigeria declined to accept jurisdiction. *Id.*

21. *Abdullahi v. Pfizer, Inc.*, 77 F. App’x 48, 52 (2d Cir. 2003).

22. *Id.* at 52.

23. *Id.* at 53.

24. See Sheryl Gay Stolberg, *U.S. AIDS Research Abroad Sets Off Outcry Over Ethics*, N.Y. TIMES, Sept. 18, 1997, at A1.

patients in developing countries.<sup>25</sup> Many African nations, suffering from a growing AIDS epidemic, permitted the scientists to conduct the “short course” Zidovudine (AZT) vaccine trials on uninformed and unwilling subjects.<sup>26</sup> The trials tested oral AZT’s effectiveness in stopping the transfer of HIV from pregnant mother to child.<sup>27</sup> Together, the CDC and NIH funded testing of more than 17,000 pregnant women, half of whom received only a placebo.<sup>28</sup>

The subjects of the study understood little about the testing, the effectiveness and possible dangers of the vaccine, and the nature of a placebo.<sup>29</sup> One journalist detailed the following account of the consent procedure used with Siata Ouattara, a subject in the study:

Minutes after [Ms. Ouattara] was informed for the first time that she carried the virus, [the] pregnant woman . . . still visibly shaken by the news, was quickly walked through the details of the tests . . . . In less than five minutes, in which the previously unknown concept of a placebo was briefly mentioned, the session was over, and Ms. Ouattara, unemployed and illiterate, had agreed to take part in the tests. Asked what had persuaded her to do so, she responded, “[t]he medical care that they are promising me.”<sup>30</sup>

Unemployment and illiteracy are not the only factors that make target groups vulnerable to exploitative research. In fact, at least one participant in the AZT trials in Africa even had a degree in law.<sup>31</sup> The researchers never explained to her that AZT had been discovered prior to these tests to block transmission of the virus during pregnancy: “I am not sure that I understood all of this so well . . . . But there were some medicines that they said might protect the mother and the child, and they wanted to follow the evolution of my pregnancy and the effectiveness of the treatment.”<sup>32</sup> Urgency also played a part: “At the time they explained this to me, I asked myself the simple question of whether I had any choice . . . . As long as there was a possibility to save my daughter, I had to try.”<sup>33</sup> Clearly, subjects of these

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25. Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT’L L. 513, 517 (2002).

26. *Id.* Participating African countries included Ivory Coast, Uganda, Tanzania, South Africa, Ethiopia, Burkina Faso, Malawi, and Zimbabwe. Michael Brown, *Medical Group Condemns U.S. AIDS Drug Tests in Africa for Using Placebo*, WASH. POST, Apr. 23, 1997, at A14.

27. Meier, *supra* note 25, at 517.

28. *Id.* at 517-18.

29. See Howard W. French, *AIDS Research in Africa: Juggling Risks and Hopes*, N.Y. TIMES, Oct. 9, 1997, at A1; Joe Stephens, *Where Profits and Lives Hang in Balance; Finding an Abundance of Subjects and Lack of Oversight Abroad, Big Drug Companies Test Offshore to Speed Products to Market*, WASH. POST, Dec. 17, 2000, at A1.

30. French, *supra* note 29, at A1.

31. *Id.*

32. *Id.*

33. *Id.*

tests are not always deceived or holding false hope; rather, they recognize that these tests represent their only option for treatment.

In 1998, the CDC abruptly announced the end of its short course AIDS vaccine research in Africa, citing the adequacy of results obtained from similar research conducted in Thailand.<sup>34</sup> Proponents of these tests argued that critics are “calling on people’s emotions rather than dealing with the facts . . . .”<sup>35</sup> Supporters of the trials included NIH head Harold Varmus, CDC head David Satcher, and the executive director of the World Health Organization Global Program on AIDS, Michael Merson.<sup>36</sup> Helene Gayle, the director of the CDC’s National Center for HIV, STD, and TB Prevention, argued that the women in these tests would not have access to any effective treatment for HIV outside of these studies.<sup>37</sup> Furthermore, cultural relativists argue that to require developing countries to adopt Western standards of informed consent is “ethical imperialism.”<sup>38</sup> Some doctors from host countries have asserted that “Americans should not impose their standards of care on developing countries,” and that “local health experts, bioethicists and affected groups are best qualified to judge the risks and benefits of any medical research.”<sup>39</sup>

The *Abdullahi* case and the African trials underscore the legal and ethical dilemmas attached to clinical trials in developing countries.<sup>40</sup> The Nigerian children and their parents never provided truly informed consent, but the subjects of these experiments deserve protection from exploitative studies. Furthermore, with Western companies and governments funding and benefiting from these experiments, developing countries become the victim in a parasitic relationship. The remainder of this Comment examines what measures are currently in place to protect human subjects of clinical trials in developing countries, followed by recommendations for what can be done to improve those measures.

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34. Joanne Roman, *U.S. Medical Research in the Developing World: Ignoring Nuremberg*, 11 CORNELL J.L. & PUB. POL’Y 441, 447 (2002). The first available results of all the studies were those from Thailand. *Id.*

35. Daniel Q. Haney, *Out Front: Journal Questions Ethics of Study to Stop Infant AIDS*, ASSOCIATED PRESS, Sept. 17, 1997.

36. Roman, *supra* note 34, at 447.

37. Susan Okie, *Researchers Assailed for AIDS Studies on Pregnant Women in Third World*, WASH. POST, Sept. 18, 1997, at A13.

38. *E.g.*, Ileana Dominguez-Urban, *Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally*, 30 CORNELL INT’L L.J. 245, 280 (1997); Lisa H. Newton, *Ethical Imperialism and Informed Consent*, IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH, May-June 1990, at 10.

39. Joseph Saba & Arthur Ammann, Editorial, *Drug Tests Offer Hope to Victims*, ARIZ. REPUBLIC/GAZETTE, Sept. 23, 1997, at B7.

40. Mary Pat Flaherty et al., *Testing Tidal Wave Hits Overseas; On Distant Shores, Drug Firms Avoid Delays—and Scrutiny*, WASH. POST, Dec. 18, 2000, at A1; Sharon LaFraniere et al., *The Dilemma: Submit or Suffer; ‘Uninformed Consent’ is Rising Ethic of the Drug Test Boom*, WASH. POST, Dec. 19, 2000, at A1.

## II. INTERNATIONAL STANDARDS FOR MEDICAL RESEARCH ON HUMAN BEINGS

The plaintiffs in *Abdullahi* alleged violations of the Code, the Declaration, and Article 7 of the ICCPR. In addition to the standards mentioned in *Abdullahi*, Part Two discusses the guidelines jointly produced by the World Health Organization's Council for International Organizations of Medical Societies (CIOMS), as well as the domestic regulations promulgated by the United States Department of Health and Human Services (HHS).

### A. The Nuremberg Code

The Code established the first international principle defining permissible medical experiments.<sup>41</sup> In *United States v. Karl Brandt*, the Nuremberg Tribunal ("Tribunal") laid out the standards now known as the Nuremberg Code.<sup>42</sup> *Brandt* found several Nazi physicians guilty of war crimes and crimes against humanity in the aftermath of World War II.<sup>43</sup> Dr. Karl Brandt led many German doctors in experiments on otherwise healthy subjects.<sup>44</sup> These experiments included submerging people in freezing water for three hours, injecting subjects with malaria, and shooting people with poisoned bullets.<sup>45</sup> The Tribunal condemned the acts of the physicians, noting that "in every single instance appearing in the record, subjects were used who did not consent to the experiments . . . it is not even contended that the subjects occupied the status of volunteers."<sup>46</sup>

The Code uses ten principles to delimit permissible medical experimentation on human subjects.<sup>47</sup> Each principle protects individual rights over researchers' needs to conduct scientific experiments.<sup>48</sup> The driving principle of the Code is informed consent. The first principle of the Code states that "[t]he voluntary consent of the human subject is absolutely essential."<sup>49</sup> This principle goes on to explain what constitutes voluntary consent and is the longest of the ten provisions.<sup>50</sup> Voluntary consent must be obtained "without the intervention" of "force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or

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41. Meier, *supra* note 25, at 523.

42. See 2 Trials of War Criminals Before the Nuernberg Military Tribunals Under Control Council Law No. 10, at 181-82 (William S. Hein & Co., Inc. 1997) (1949) [hereinafter Nuremberg Code].

43. Meier, *supra* note 25, at 522-23.

44. *Id.* at 521.

45. *Id.*

46. Nuremberg Code, *supra* note 42, at 183.

47. *Id.* at 181-82.

48. Roman, *supra* note 34, at 448.

49. Nuremberg Code, *supra* note 42, at 181.

50. *Id.* at 181-82.

coercion . . . .”<sup>51</sup> The subject is to be informed of the “methods and means” of the test and of “all inconveniences and hazards reasonably to be expected . . . .”<sup>52</sup> A plain reading of the first principle of the Nuremberg Code reveals it to require a complete description of the test and untainted and completely voluntary consent. It requires a “true understanding” of the procedure.<sup>53</sup>

Informed consent, however, is not the only precept of the Nuremberg Code. The majority of the remaining provisions concern the welfare of the research subject.<sup>54</sup> These requirements include the creation of a valid research design seeking otherwise unobtainable information that is important for the good of society, the avoidance of unnecessary suffering, the lack of an a priori reason to believe that death or injury may occur, the determination that benefits outweigh the possible risks, and the duty of the researcher to terminate the experiment if it “is likely to result in injury, disability, or death . . . .”<sup>55</sup>

### B. *The Declaration of Helsinki*

The medical community first set forth its own criteria “to provide guidance to physicians . . . in medical research involving human subjects” with the Helsinki Declaration.<sup>56</sup> The World Medical Association issued the Declaration in 1964 and revised it most recently in 2000.<sup>57</sup> The Declaration requires informed consent and places a duty on the physician to “promote and safeguard the health of the people.”<sup>58</sup> The Declaration explains that after ensuring the subject understands the details of the research, the physician should obtain the subject’s “freely-given consent, preferably in writing.”<sup>59</sup> At the least, the Declaration requires that the consent should be formally documented and witnessed.<sup>60</sup> The Declaration recognizes that some research populations “are vulnerable and need special protection.”<sup>61</sup> Particular vulnerabilities are again recognized in Principle Twenty-Three, which explains that a physician should be cautious when obtaining

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51. *Id.* at 181.

52. *Id.* at 182.

53. Roman, *supra* note 34, at 449.

54. Nuremberg Code, *supra* note 42, at 182. The 9th establishes the right of patients to end participation at any time during the experiment. *Id.*

55. *Id.*

56. 52nd WMA General Assembly, *World Medical Association Declaration of Helsinki*, § A.1 (Oct. 2000), <http://www.wma.net/e/policy/pdf/17c.pdf> [hereinafter *Declaration*]; Kelleher, *supra* note 4, at 74.

57. Kelleher, *supra* note 4, at 74.

58. *Declaration*, *supra* note 56, at §§ A2, B22-24, B26.

59. *Id.* § 22.

60. *Id.*

61. *Id.* § 8.



informed consent if the subject is in a dependent relationship with the physician.<sup>62</sup> The Declaration also provides that there should be a “reasonable likelihood” that the research population stands to benefit from the results of the research.<sup>63</sup>

Furthermore, the Declaration provides for several other layers of protection from unethical patient exploitation. First, it identifies the need for independent ethical review committees to ensure “conformity with the laws and regulations of the country in which the experiment is performed.”<sup>64</sup> Part C of the Declaration is titled, “Additional Principles for Medical Research Combined with Medical Care.”<sup>65</sup> Here, the Declaration distinguishes between therapeutic and non-therapeutic research.<sup>66</sup> This section also explains that the physician “may combine medical research with medical care.”<sup>67</sup> However, the Declaration cautions that when this situation occurs, “additional standards apply to protect the patients who are research subjects.”<sup>68</sup>

### C. *International Covenant on Civil and Political Rights*

The ICCPR<sup>69</sup> is the only legally binding international treaty concerning human experimentation.<sup>70</sup> In Article 7 of the ICCPR, the United Nations incorporated the informed consent principle in the context of human experimentation.<sup>71</sup> Article 7 specifies that “[n]o one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.”<sup>72</sup>

### D. *WHO-CIOMS Guidelines*

In 1982, the World Health Organization and Council for International Organization of Medical Sciences published the *Proposed International Ethical Guidelines for Biomedical Research involving Human Subjects* (“Guidelines”).<sup>73</sup>

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62. *Id.* § 23.

63. *Id.* § 19.

64. *Id.* § 13.

65. *Id.* §§ 28-32.

66. *Id.* § 28.

67. *Id.*

68. *Id.*

69. International Covenant on Civil and Political Rights, Dec. 19, 1966, 999 U.N.T.S. 171 (entered into force March 23, 1976) [hereinafter ICCPR].

70. Kelleher, *supra* note 4, at 73. Ratifying states must comply with the terms of the treaty. ICCPR, *supra* note 69, art. 50.

71. *See* ICCPR, *supra* note 69, at 175.

72. *Id.*

73. Council for Int’l Org. of Med. Sci. (CIOMS), in collaboration with the World Health Organization (WHO), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002) [hereinafter *Guidelines*].

They were revised in 1993 and again in 2002 to address current issues, such as the AIDS epidemic.<sup>74</sup> The Guidelines were intended to be a prototype for nations drafting legislation on human research.<sup>75</sup> Under the subtitle "General Ethical Principles," the Guidelines mandate that "[a]ll research involving human subjects should be conducted in accordance with three basic ethical principles . . . respect for persons, beneficence and justice."<sup>76</sup>

The Guidelines identify pregnant and nursing women, prisoners, children, and persons with mental or behavioral disorders as vulnerable to nonconsensual experimentation.<sup>77</sup> The General Ethical Principles also explain that the subjects selected should be the least vulnerable necessary to accomplish the purposes of the research.<sup>78</sup> Guideline 13 requires special justification for inviting vulnerable individuals to serve as research subjects.<sup>79</sup> The commentary to this guideline defines vulnerable persons as "those who are relatively (or absolutely) incapable of protecting their own interests."<sup>80</sup> This may include those who have "insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests."<sup>81</sup>

The Guidelines, like the Declaration, discuss the role of ethical review boards. Yet where the Declaration suggests that it may be necessary, the Guidelines mandate an ethical review of human testing. The Guidelines instruct ethical review boards to approve or reject research protocols before proceeding with research.<sup>82</sup> Guideline 2 specifies that "[a]ll 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."<sup>83</sup> This guideline additionally requires that the review committees be independent of the research team, and whatever financial benefit they receive must not be contingent on the outcome of their review.<sup>84</sup> Furthermore, the guideline provides for committee review "as necessary" throughout the course of the research.<sup>85</sup>

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74. *Id.* at 7-10.

75. Meier, *supra* note 25, at 526-27.

76. *Guidelines*, *supra* note 73, at 17.

77. *Id.* at 64-65, 74.

78. *Id.* at 18.

79. *Id.* at 64.

80. *Id.*

81. *Id.*

82. *Id.* at 24.

83. *Id.*

84. *Id.*

85. *Id.*

Guideline 4 requires individual informed consent for all biomedical research involving humans.<sup>86</sup> The commentary to this guideline goes on to explain what should be done with respect to the process, language, comprehension, documentation, and cultural considerations involved with informed consent.<sup>87</sup> Guidelines 5, 6, and 7 also relate to informed consent and discuss essential information for prospective research subjects, obligations of sponsors and investigators, and inducement to participate.<sup>88</sup> Continuing to echo the previous contemplations, these guidelines require that the investigator ensure that the potential benefits and risks “are reasonably balanced” and “risks are minimized.”<sup>89</sup>

The Guidelines further require:

[b]efore undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that: the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.<sup>90</sup>

As the commentary explains, this part addresses populations that are “vulnerable to exploitations by sponsors and investigators from the relatively wealthy countries and communities.”<sup>91</sup> Guideline 10 goes beyond the previous recognitions of vulnerability to encompass socioeconomic defenselessness.

#### *E. Domestic Regulations of Human Experimentation*

Title 45 of the Code of Federal Regulations, Part 46, “Protection of Human Subjects,” serves as HHS’s ethical guidelines for human experimentation in the United States.<sup>92</sup> The Food and Drug Administration (FDA) also has regulations governing human experimentation, and they are substantially similar to the HHS regulations.<sup>93</sup> The FDA regulations apply to all clinical investigations that support applications for research or marketing permits for products regulated by the FDA.<sup>94</sup> HHS’s Office for Human Research Protection (OHRP) has the primary responsibility within the United States government for developing and implementing the policies, procedures, and regulations to protect human subjects

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86. *Id.* at 32.

87. *Id.* at 32-34.

88. *Id.* at 37-46.

89. *Id.* at 47.

90. *Id.* at 51.

91. *Id.*

92. 45 C.F.R. § 46 (2005).

93. 21 C.F.R. § 50 (2005).

94. *Id.* § 50.1 (2005).

involved in research sponsored by HHS.<sup>95</sup> The OHRP has set up formal agreements with more than 4,000 federally funded universities, hospitals, and other medical research institutions in the United States and abroad.<sup>96</sup>

Each institution is required to establish one or more institutional review boards (IRBs).<sup>97</sup> The IRBs “are responsible for ensuring that people who agree to participate in studies fully understand the nature of the research and willingly consent to participate.”<sup>98</sup> The regulations list seven requirements in order for research to be approved.<sup>99</sup> These regulations include the minimization of risk, making risks reasonable in relation to anticipated benefits, equitable selection of subjects, and the pursuit and documentation of informed consent.<sup>100</sup>

To satisfy informed consent, potential participants are to be given an explanation of the purposes of the research, the expected duration of their participation, and a description of the procedure.<sup>101</sup> Researchers are also required to inform the subject that the study involves research, as well as identify any procedures which are experimental.<sup>102</sup> Furthermore, the subject must be informed of foreseeable risks and there must be a disclosure of appropriate alternative procedures and courses of treatment.<sup>103</sup>

The HHS regulations also specifically address research conducted in foreign countries.<sup>104</sup> Section 46 acknowledges that procedures in foreign countries often differ from those promulgated by HHS.<sup>105</sup> As an example, the regulation refers to a “foreign institution which complies with guidelines consistent with [the Declaration of Helsinki] . . . .”<sup>106</sup> In such a circumstance, as long as a “department or agency head” decides that the procedures are at least equivalent to HHS’s, then

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95. Press Release, U.S. Dep’t of Health & Human Servs., New Office for Human Research Protections Created, Dr. Greg Koski Named Director (June 6, 2000) [hereinafter New Office], <http://www.hhs.gov/news/press/2000pres/20000606.html>. The HHS regulations apply to all research conducted or supported by the federal government. 45 C.F.R. § 46.101 (2004).

96. *Id.*

97. 45 C.F.R. § 46.103(b)(2) (2004).

98. Press Release, U.S. Dep’t of Health & Human Servs., Protecting Human Research Subjects (June 6, 2000) [hereinafter Protecting Human Research Subjects], <http://www.hhs.gov/news/press/2000pres/20000606a.html>.

99. 45 C.F.R. §§ 46.111(a)(1) – (5) (2004).

100. *Id.* The last two criteria require that, when appropriate, “the research plan makes adequate provision for monitoring data collected to ensure the safety of subjects” and that “there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.” 45 C.F.R. §§ 46.111(a)(6) & (7) (2004).

101. 45 C.F.R. § 46.116(a)(1) (2004).

102. *Id.*

103. 45 C.F.R. §§ 46.116(a)(2) & (4) (2004).

104. *Id.* § 46.101(h) (2004).

105. *Id.*

106. *Id.*

the foreign procedures may be used.<sup>107</sup> OHRP also recognizes the additional protections needed for vulnerable populations.<sup>108</sup> In order for an IRB to approve research on subjects that are likely to be vulnerable to coercion or who are economically or educationally disadvantaged, additional safeguards must be included.<sup>109</sup>

The various guidelines and recommendations governing human experimentation vary depending on the source. There are certain features, however, that appear constant. First, every scheme requires that research must conform to some kind of informed consent principles; participants should generally be aware of the nature of the trial and be free to choose whether to participate. Second, all of the schemes include some type of balancing test where the benefits must outweigh the risks. Finally, minimum standards of care are required and certain vulnerable populations must be protected.

### III. IDENTIFICATION AND ANALYSIS OF GAPS IN HUMAN EXPERIMENTATION STANDARDS

The medical tests conducted by Pfizer and the CDC demonstrate that the current guidelines for human experimentation are not adequate. This Part identifies the gaps and problems in the existing regulations in order to offer potential remedies. Specifically, this section will focus on four areas: informed consent, the vulnerable patient, benefit analyses, and enforceability.<sup>110</sup>

#### *A. Informed Consent*

Informed consent must walk the line between being too permissive and being too strict. The line must balance on either end the danger of threatening individual autonomy and the danger of restricting medical progress. When addressing informed consent, the Declaration leans toward being overly permissive, while the Code is often viewed as too strict. Researchers criticize the Code as “too uncompromising and too inhospitable to the advancement of science.”<sup>111</sup> The

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107. *Id.*

108. 45 C.F.R. § 46.111(b) (2004).

109. *Id.*

110. A complete analysis would encompass a number of other areas, but due to space considerations these four areas are highlighted.

111. Ruth Macklin, *Universality of the Nuremberg Code*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* 235 (George J. Annas & Michael A. Grodin eds., 1992); see also Kelleher, *supra* note 4, at 73.

Declaration, on the other hand, is often criticized for looking at human experimentation with too much emphasis on scientific progress.<sup>112</sup>

The Code represents a reaction to Nazi Germany's forced human experimentation<sup>113</sup> and therefore does not at all emphasize the need for medical progress. The first principle of the Code makes clear that the focus is on the voluntariness of the subject.<sup>114</sup> This principle explains voluntariness as having the "legal capacity to give consent" and requires that the person should be "so situated as to be able to exercise free power of choice, without intervention of any element of force, fraud, deceit, [or] duress . . ." <sup>115</sup> In focusing so heavily on the necessity of voluntary consent, the Code does not consider the potential detrimental effect on medical progress. For instance, requiring all subjects to have the "legal capacity" to consent removes a large section of potentially helpful medical subjects. Lacking the "legal capacity" means that children are essentially off-limits to researchers.

Critics of the Code argue that it impedes medical progress because it does not account for hardship in obtaining informed consent in complicated experiments not fully understood by patients.<sup>116</sup> Furthermore, critics argue that the Code does not consider cultural variations about what constitutes consent.<sup>117</sup> Some cultures preserve the roles of decision-making affecting the public good by only allowing leaders of the community to make or supplement individual consent decisions.<sup>118</sup> The Code's rigidity makes it unfavorable in both the medical community and developing countries.<sup>119</sup>

The Declaration represents a reaction to what physicians viewed as the Code's deficiencies.<sup>120</sup> Many physician-researchers believed that the Code was inapplicable to their own practices and that it only applied to war crimes committed by pseudo-scientists.<sup>121</sup> Thus, the Declaration clearly focuses more on the interests of researchers. The Declaration makes this clear when, before it mentions the rights or autonomy of human subjects, it focuses on the physician and

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112. E.g., David M. Carr, *Pfizer's Epidemic: A Need for International Regulation of Human Experimentation in Developing Countries*, 35 CASE W. RES. J. INT'L L. 15, 47 (2003).

113. See Michael A. Grodin, *Historical Origins of the Nuremberg Code*, in THE NAZI DOCTORS, *supra* note 111, at 137-38.

114. Nuremberg Code, *supra* note 42, at 181.

115. *Id.*

116. E.g., Carr, *supra* note 112, at 31.

117. *Id.*; see also Meier, *supra* note 25, at 525-26.

118. E. Maxine Ankrah & Lawrence O. Gostin, *Ethical and Legal Considerations of the HIV Epidemic in Africa*, in AIDS IN AFRICA 548 (Max Essex et al. eds., 1994).

119. Carr *supra* note 112, at 32.

120. George J. Annas, *The Changing Landscape of Human Experimentation: Nuremberg, Helsinki and Beyond*, 2 HEALTH MATRIX 119, 122 (1992).

121. David J. Rothman, *Bringing Ethics to Human Experimentation: The American Experience*, in RESEARCH ON HUMAN SUBJECTS: ETHICS, LAW AND SOCIAL POLICY 35-36 (David N. Weisstub ed., 1998).

the significance of medical progress. The fourth paragraph of the Declaration states that “[m]edical progress is based on research which ultimately must rest in part on experimentation involving human subjects.”<sup>122</sup> Then, sixteen paragraphs later, the Declaration states that “subjects must be volunteers and informed participants in the research project.”<sup>123</sup> This separation emphasizes the shifted focus from the subject’s rights in the Code to the recognition of the importance of medical progress in the Declaration.

Departing from the standard of the Code, the Declaration lightens the informed consent burden on researchers. The Declaration allows for research on legally incompetent individuals if consent is obtained from a legally authorized representative.<sup>124</sup> Furthermore, while the Code does not allow consent resulting from duress,<sup>125</sup> the Declaration opens the window slightly. According to the Declaration, consent may be given under duress as long as the consent is “obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of [the researcher-subject] relationship.”<sup>126</sup> The Declaration also waives consent where the “physical/mental condition [of the subject] that prevents obtaining informed consent is a necessary characteristic of the research population.”<sup>127</sup>

In some respects, the Declaration also heightens the informed consent requirements. Unlike the Code, the Declaration states that it is the duty of the physician to inform the subject of the “aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher and the anticipated benefits . . . of the study.”<sup>128</sup> However, this apparently heightened requirement is somewhat deceiving. Although this requirement provides more detail than the Code as to what a subject should know, it fails to require that the researcher inform the subject that the research is an experiment.<sup>129</sup> At best, the

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122. *Declaration, supra* note 56, § 4.

123. *Id.* § 20.

124. *Id.* § 24.

125. Nuremberg Code, *supra* note 42, at 181.

126. *Declaration, supra* note 56, § 23.

127. *Id.* § 26.

128. *Id.* § 22.

129. Paragraph 22 of the Declaration of Helsinki provides in full:

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely-given consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed. *Id.*

information required to be imparted to the subject could result in the *inference* that she is participating in an experiment.

David Carr argues that the Declaration leaves open the possibility of community consent in lieu of individual consent, while the Code and Guidelines clarify that individual consent is always required. He asserts that a patient may inadvertently volunteer to be part of a research experiment.<sup>130</sup> According to Carr, “subjects entering into facilities where medical treatment is being provided to those in need by charitable organizations could easily mistake the experimental research, thus disposing of the need for researchers to obtain consent.”<sup>131</sup> This is exactly what happened when Pfizer went to Kano, Nigeria.<sup>132</sup> Patients were not aware that they could receive adequate treatment from Doctors Without Borders (MSF), which was set up adjacent to Pfizer.<sup>133</sup> Carr argues that the Declaration does not require individual consent from subjects in a community subscribing to community consent.<sup>134</sup> Thus, under the Declaration, the Kano researchers may be viewed as having obtained informed consent because the community consented to the research.<sup>135</sup>

The Guidelines take a more balanced approach to informed consent than the Declaration and the Code. The Guidelines do not banish all experimentation on the legally incompetent.<sup>136</sup> Rather, they permit “legally authorized representative[s]” to provide consent on their behalf.<sup>137</sup> The Guidelines also allow for a waiver of informed consent in “uncommon and exceptional” situations.<sup>138</sup> The commentary clarifies that informed consent may be waived when the risks are minimal and obtaining informed consent makes the research impracticable.<sup>139</sup> Unlike the Declaration, the Guidelines require the subject be informed that she has been invited to participate in research.<sup>140</sup> Yet, similar to the Declaration, the Guidelines require disclosure of the purpose of the research and the institutional affiliation of the researcher.<sup>141</sup>

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130. Carr, *supra* note 112, at 34.

131. *Id.*

132. *Abdullahi v. Pfizer, Inc.*, No. 01 Civ. 8118, 2002 U.S. Dist. LEXIS 17436, at \*3 (S.D.N.Y. Sept. 16, 2002).

133. *Id.*

134. Carr, *supra* note 112, at 34.

135. *Abdullahi*, 2002 U.S. Dist. LEXIS 17436, at \*3 (noting that Pfizer obtained consent from both the Nigerian government and the staging hospital’s ethics committee permitting the export of Trovan to Kano).

136. *Guidelines*, *supra* note 73, at 32.

137. *Id.*

138. *Id.*

139. *Id.*

140. *Id.*

141. *Id.* at 37.



Like both the Code and the Declaration, the Guidelines do not directly address community consent. However, the commentary to Guideline 4 does indicate that community consent may play a role in informed consent.<sup>142</sup> The commentary acknowledges that some cultures only allow researchers to enter their community or obtain individual consent after the community leader consents.<sup>143</sup> The commentary acknowledges that these customs must be respected but still requires individual consent to be obtained.<sup>144</sup> The HHS regulations also allow for cultural considerations when addressing research conducted in foreign countries.<sup>145</sup> These regulations, however, are open-ended in terms of what types of policies can be used in lieu of the HHS regulations.<sup>146</sup>

The various schemes governing human experimentation make clear that effective guidance regarding informed consent must consider a number of factors. Broadly speaking, the protection of human subjects must be examined in relation to the interest of medical advancement. Just as informed consent should not be so strict as to limit medical advancement, it should neither be so loose as to invade individual autonomy. Also significant is the level at which cultural considerations come into play. Except for the Code, all of the schemes seem to acknowledge cultural differences to some extent, but there is no guidance on how to address the cultural differences. An ideal international standard should recognize varying consent customs, but also require individual consent. This would simultaneously respect the foreign culture and not invade individual autonomy.

### *B. The Vulnerable Patient*

Informed consent is not a “one-size-fits-all” concept. Medical research in developing countries is an issue precisely because their populations are often vulnerable to exploitation, despite efforts to promote and use informed consent.<sup>147</sup> Therefore, an examination of international guidelines must include an inquiry into how the various schemes recognize certain vulnerabilities. Again, this must be done within the balancing framework, with potential exploitation on one side and halting medical progress on the other.

The Code’s strictness and sparseness bar a meaningful consideration of vulnerability. Although strict requirements may initially seem beneficial to a vulnerable population, this is not necessarily the case. The first statement of the Code prohibits use of human subjects where the patients may be under duress or

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142. *Id.* at 35.

143. *Id.*

144. *Id.*

145. 45 C.F.R. § 46.101(h) (2004).

146. *Id.* (allowing other protections to supersede those provided by HHS, but failing to explain which other protections would be appropriate).

147. *See supra* notes 13-14, 30-33 and accompanying text.

coercion.<sup>148</sup> These factors implicitly acknowledge the vulnerability of certain individuals, but nothing expressly recognizes this potential vulnerability.<sup>149</sup> This omission is dangerous to vulnerable populations because their consent may be more easily obtained. When a population has no other options for medical treatment, they may more readily give their informed consent despite the risks.

The Declaration more explicitly acknowledges vulnerability, but it does not do enough. Paragraph 8 recognizes that “[s]ome research populations are vulnerable and need special protection.”<sup>150</sup> The Declaration does not anywhere else use the phrase “vulnerable population,” but it does refer to those who are “legally incompetent, physically or mentally incapable of giving consent.”<sup>151</sup> Regarding such vulnerabilities, the Declaration requires that the investigator defer to local law.<sup>152</sup> Local law in developing countries, however, is not generally going to be adequate to appropriately address vulnerability concerns.<sup>153</sup>

The Guidelines go into more detail about vulnerable populations and explicitly discuss which populations constitute vulnerable populations. Vulnerable classes consist of those with “limited capacity or freedom to consent or to decline consent. They . . . include children, and persons who because of mental or behavioral disorders are incapable of giving informed consent.”<sup>154</sup> Guideline 13 covers “research involving vulnerable persons” and specifies that “special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.”<sup>155</sup> The comment to Guideline 13 lists a series of elements constituting special justification:

the research could not be carried out as well with less vulnerable subjects;

the research is intended to obtain knowledge that will lead to improved diagnosis prevention or treatment of diseases characteristic of the vulnerable class;

subjects will be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;

the risks will not exceed those associated with routine medical examination of such persons; and

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148. Nuremberg Code, *supra* note 42, at 181.

149. *Id.*

150. *Declaration*, *supra* note 56, § 8.

151. *Id.* § 24.

152. *Id.*

153. *See Carr*, *supra* note 112, at 42.

154. *Guidelines*, *supra* note 73, at 64.

155. *Id.*

when prospective subjects are either incompetent or otherwise unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.<sup>156</sup>

Missing from the definition of vulnerable persons are “populations and communities with limited resources.”<sup>157</sup> The Guidelines do not deem this category of people “vulnerable.” Rather, this class of people is separated from those who are vulnerable and addressed in Guideline 10. This Guideline requires that to conduct research in a population with limited resources, the research must be responsive to the health needs of the population and that any product developed or knowledge generated will be made available for the benefit of that population.<sup>158</sup>

Although Guideline 10 avoids using “vulnerable” to describe populations with limited resources, the subsequent commentary does not manage the same.<sup>159</sup> The commentary explains that “this guideline is concerned with . . . communities in which resources are limited to the extent that they are, or may be, *vulnerable to exploitation* by sponsors and investigators from the relatively wealthy countries and communities.”<sup>160</sup> There appears to be a disparity, then, between the ways various classes of vulnerable populations are treated. The vulnerable populations addressed in Guideline 13 have the extra protection of “special justifications” for participation in research.<sup>161</sup> There is nothing in the Guidelines that explains the difference between the various classes of vulnerability.

The Declaration also never explicitly identifies populations and communities with limited resources as vulnerable.<sup>162</sup> In fact, the Declaration’s identification of vulnerable populations resembles the definition in the Guidelines.<sup>163</sup> The omission of communities with limited resources may be explained away by a lack of foresight; however, there may be other reasons for the distinction as well. For instance, the first requirement for special justification under Guideline 13 is that the research could not be carried out as well with less vulnerable subjects.<sup>164</sup> Applying this standard to developing countries may be harmful. As stated previously, these medical trials may be certain populations’ only available access

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156. *Id.* at 64-65.

157. *Id.*

158. *Id.* at 51.

159. *Id.* at 51-53.

160. *Id.* at 51 (emphasis added).

161. *See id.* at 51-53.

162. *Declaration, supra* note 56, § 8.

163. Both the Helsinki Declaration and the Guidelines focus on groups of people who are legally or physically incompetent to give consent. *Id.* at §§ 24-26; *Guidelines, supra* note 73, at 64.

164. *Guidelines, supra* note 73, at 64.

to treatment.<sup>165</sup> Therefore, it may be harmful to require that research be conducted elsewhere if possible. Ideally, researchers should recognize the benefits their research may confer to vulnerable populations. If properly regulated, researchers should not be *discouraged* from conducting research on vulnerable populations, but rather, *encouraged*.

The HHS regulations also identify vulnerable populations, but the regulations lack the detail of the Guidelines.<sup>166</sup> Vulnerable persons under the HHS regulations may include children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.<sup>167</sup> This definition, unlike the Guidelines, lumps together the economically disadvantaged with those who may be unable to legally or mentally provide consent.<sup>168</sup> The HHS regulations are not specific about how to handle economically or educationally disadvantaged populations.

The various schemes demonstrate that it is not always clear how to treat vulnerable populations. This is true for a number of reasons. First, it is not always evident what classes of people constitute a vulnerable population. Second, once a vulnerable population is determined, it is not clear which procedures would be the most appropriate in terms of medical testing. An improved international standard must distinguish between communities lacking resources and individuals incapable of providing consent. Incompetence and poverty are not interchangeable. Distinguishing between these two areas leads to the next step for an improved international standard that develops appropriate procedures to protect the various vulnerable populations. Once they are identified, an improved international standard should require researchers to specify when they are researching a vulnerable population, thus triggering specific protective guidelines.

### C. Benefits

Ultimately, the goal of medical testing is to achieve some type of benefit. Once an improved standard identifies a vulnerable population, part of protecting that population includes assuring that some type of benefits accrue to the population. These benefits encompass profitability, medicines and products, the advancement of medical knowledge, and improved health. Discussing benefits in the context of medical testing in developing countries becomes controversial because their populations are generally not the beneficiaries of medical advancement.<sup>169</sup> This contributes to the perception that developing countries are being exploited to the benefit of the developed world. All of the schemes

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165. *Supra* notes 30-33 and accompanying text.

166. *See* 45 C.F.R. § 46 (2004).

167. 45 C.F.R. §§ 46.111(a)(3) & (b) (2004).

168. *Id.*

169. *See Fair Benefits, supra* note 3, at 2133.

governing human experimentation address benefits, but how to allocate those benefits is not apparent.

Unsurprisingly, the Code does not address benefits to any great extent.<sup>170</sup> The sixth principle of the Code requires that the “degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”<sup>171</sup> Benefits are only discussed within this risk/benefit balancing test.<sup>172</sup> The Code does not consider to whom the benefits will accrue, but only establishes that “humanitarian importance” outweighs degree of risk.<sup>173</sup> Although this may have adequately addressed the war crimes to which the Code responds, it is not sufficient for current trends in medical testing.

The Declaration also considers benefits and, unlike the Code, considers the beneficiaries. The Declaration requires “special attention” for those who will not personally benefit from the research.<sup>174</sup> This statement implies that the Declaration acknowledges the potential for exploitation of groups who do not stand to benefit from the research. The Declaration also provides a cost/benefit provision similar to the Code’s; it specifies that physicians “should cease any investigation if the risks are found to outweigh the potential benefits.”<sup>175</sup> The Declaration does not discuss, however, whether benefits should ever necessarily accrue to the tested populations. This gap once again reflects the Declaration’s physician-centered view.<sup>176</sup>

The Guidelines discuss this issue in more detail. Guideline 8 states that the potential benefits and risks of the study must be reasonably balanced and the risks must be minimized.<sup>177</sup> This Guideline is similar to the benefit considerations of the Code and Declaration in that it looks at benefits in the context of a cost/benefit analysis. Furthermore, the purpose of this Guideline is really to minimize risks, not to ensure benefits.<sup>178</sup> Guideline 10, discussed previously, offers the first serious look at vulnerable populations as beneficiaries.<sup>179</sup> As discussed, this

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170. Nuremberg Code, *supra* note 42, at 181-82.

171. *Id.* at 182.

172. *Id.*

173. *Id.*

174. *Declaration, supra* note 56, at § 8.

175. *Id.* § 17.

176. *See supra* note 54. It is also interesting to note that the World Medical Association, which created the Declaration, lost a great deal of credibility in 1992 when it elected Hans-Joachim Sewering, a former Nazi physician, as its president. GEORGE J. ANNAS, *SOME CHOICE: LAW, MEDICINE, AND THE MARKET* 251 (1998). Sewering resigned only after the American Medical Association produced documents that proved his involvement in the Nazi euthanasia experiments on the mentally ill. S. Con. Res. 69, 104th Cong. (1996).

177. *Guidelines, supra* note 73, at 48.

178. *Id.* at 47-49.

179. *Id.* at 51.

Guideline specifies that the research population must benefit from the “product developed, or knowledge generated.”<sup>180</sup>

Ensuring that the host community benefits from the research is not simple, as the commentary to Guideline 10 makes clear.<sup>181</sup> The commentary explains that investigating “reasonable availability” should include negotiations with “representatives of stakeholders in the host country; these include the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which subjects are drawn and non-governmental organizations such as health advocacy groups.”<sup>182</sup> The commentary further states that if the tested drug proved beneficial to the subjects, the sponsor should continue to provide it to them after the conclusion of the study.<sup>183</sup> The Guidelines give a much clearer picture of what it means to benefit the host population. What is not entirely clear is how to effect the benefit, and whether the benefit contemplated is even feasible.

The Guidelines’ reasonable availability approach is not without its critics. Critics argue that reasonable availability fails to guarantee that benefits are distributed fairly, especially when there are large gains to the entities sponsoring the research, as well as high risks.<sup>184</sup> Furthermore, reasonable availability only succeeds in Phase III research that produces an effective outcome; it does not apply to Phase I, Phase II, or unsuccessful Phase III tests.<sup>185</sup> Therefore, reasonable availability can fail to protect against exploitation.<sup>186</sup>

Like the previous governing mechanisms, the HHS regulations also look at benefit in terms of a cost/benefit analysis. The risks to the subjects are required to be “reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”<sup>187</sup> The regulations do not address specific benefits to vulnerable populations.

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180. *Id.*

181. *Id.* at 51-53.

182. *Id.* at 52.

183. *Id.*

184. *Fair Benefits*, *supra* note 3, at 2133.

185. *Id.* A Phase I trial is an initial study to “determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.” HIV/AIDS TREATMENT INFO. SERV., GLOSSARY OF HIV/AIDS-RELATED TERMS 91 (4th ed. 2002). A Phase II trial “involves controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.” *Id.* A Phase III trial involves “[e]xpanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.” *Id.*

186. *Fair Benefits*, *supra* note 3, at 2133.

187. 45 C.F.R. § 46.111(a)(2) (2004).

These people are exploited when they reap none of the benefits from the knowledge they help achieve through their participation in medical research. To avoid this, it is necessary to formulate a way in which vulnerable populations are not mere guinea pigs in an experiment, but actual beneficiaries of medical testing. None of the governing schemes adequately address how to achieve this. An improved international standard must contemplate what benefits would be feasible and also enhance the protection of vulnerable communities. Effecting feasible and fair benefits involves looking beyond what the various international standards suggest. An improved international standard should require researchers to develop a research plan that specifies how the identified vulnerable population will benefit from the research.

#### *D. Enforceability*

The Code, Declaration, and Guidelines do not impose legally enforceable obligations on states or individuals.<sup>188</sup> The three standards do, however, carry persuasive weight in regulating doctors and finding liability.<sup>189</sup> Unfortunately, these standards may lack efficacy even as persuasive weight, because they remain inconsistent. Furthermore, the Code and the Declaration lack specificity, and researchers may consequently use their interpretive skills to extract a loose standard. Enforceability, though a lofty goal in the international context, would allow for more accountability in the arena of international human experimentation. Researchers would be more likely to construct and conduct medical trials that conform more precisely to articulated safeguards intended to protect human subjects.

The Code does not even address the need for supervision of experimental research; it never mentions IRBs or any other entity to provide oversight. The Declaration also does not provide a legal standard of enforcement for its provisions. Although the Declaration does assume that ethical oversight committees will supervise experimental research, this is not always feasible.<sup>190</sup> Often, developing countries will lack the ability and resources to maintain ethical oversight committees.<sup>191</sup> Furthermore, because the Declaration is primarily interested in protecting doctors and not patients,<sup>192</sup> enforcement is not emphasized. As one scholar put it, “[b]ecause of its one-sided approach to regulation, the

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188. International Summit Conference on Bioethics, *Towards an International Ethic for Research with Human Beings* 39 (1987).

189. Carr, *supra* note 112, at 47-48.

190. *Id.* at 45.

191. *Id.* at 45-46.

192. *See supra* note 169 and accompanying text.

Declaration does not provide adequate legal guidance to companies, but more closely resembles a field manual for procedural policy.”<sup>193</sup>

The Guidelines are similarly unhelpful in terms of enforcement. Like the Declaration, the Guidelines use ethical review committees to supervise human experimentation.<sup>194</sup> These ethical review committees generally do not have the power to impose sanctions for violations by researchers.<sup>195</sup> They are allowed, however, to deem a research project unethical and withdraw approval.<sup>196</sup> The ethical review committee is also required to report violations to local or national governments or enforcement agencies.<sup>197</sup> Ultimately, the Guidelines, like the Code and the Declaration, lack any significant enforcement features. None of the standards have the authority of binding international law.<sup>198</sup>

Not all of the international standards lack enforceability. The ICCPR, the sparsest of all the standards, is enforceable. Under Article 2, all parties to the covenant must adopt laws to give effect to the rights recognized in the ICCPR.<sup>199</sup> Furthermore, Article 2 obliges all parties to ensure that any person whose rights or freedoms are violated has an effective remedy.<sup>200</sup> However, the ICCPR, as it is, does not provide adequate requirements and procedures for medical testing. Rather, it contains only a basic statement requiring consent.<sup>201</sup>

An improved international standard should contain comprehensive procedural requirements and be enforceable. Amending the ICCPR to require more than basic consent to medical testing would be an improvement. However, efforts at enforcement should not cease at the ICCPR and may require more creativity. For instance, domestic policies and regulations also provide opportunity for improvement. Additionally, the pressure of publicity, positive or negative, may encourage improvement in international practices.

#### IV. RECOMMENDATIONS

As the *Abdullahi* case and the AZT experiments illustrate,<sup>202</sup> the current governing mechanisms do not provide the necessary protections to vulnerable

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193. Carr, *supra* note 112, at 47.

194. *Guidelines*, *supra* note 73, at 24.

195. *Id.* at 29.

196. *Id.*

197. *Id.*

198. Carr, *supra* note 112, at 48.

199. ICCPR, *supra* note 69, at 173-74.

200. *Id.* at 174.

201. *Id.* at 175 (“No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.”).

202. See discussion, *supra* Part I.



populations. An improved international standard would revise the informed consent standard, adequately define vulnerable populations, and ensure that appropriate benefits accrue to the vulnerable population. Ideally, the international community should convene a convention addressing the protection of human subjects, which would result in an enforceable treaty. Recognizing the limited feasibility of this suggestion, this Part also considers other international and domestic efforts that would improve the current trends in international human experimentation. Internationally, the ICCPR could be amended to include more detailed human experimentation provisions. Domestically, FDA and HHS regulators should require more from researchers in order to ensure that patients are informed, vulnerable populations are identified, and benefits are appropriately allocated.

The first step in creating an international standard requires a recognition that informed consent practices must be improved. Some of the most troubling facts of the *Abdullahi* case were the glaring violations of informed consent.<sup>203</sup> Most participants could not speak English, did not know that they could refuse, and did not know they could receive treatment from MSF.<sup>204</sup> An informed consent standard must ensure that the participants *understand* that the treatment is experimental. This means that a consent form must be in the relevant language—or that there be a translator (and a witness). It also requires that the patients know that they have the right to stop treatment and that other treatments are available.

These elements of informed consent are not new, as the examination of the various standards demonstrated. Informed consent standards, however, must adapt to the appropriate context. For instance, when Pfizer researchers sought consent from subjects in Nigeria, part of the consent should have involved disclosing that there was available treatment from charitable organizations. An international standard must also be flexible enough to account for different traditions and customs of consent. Specifically, if it is the tradition of the community that certain leaders consent on behalf of the population, informed consent standards should recognize that custom. The consent standard must not, however, become so flexible as to forgo obtaining individual consent. Even where community consent is given, researchers should still seek individual consent.

Furthermore, an international standard cannot ignore the reality that patients in vulnerable populations will be more willing to consent to potentially inadvisable research participation. In order to prevent exploitation, an international standard should define “vulnerable populations” and have specific requirements to address their needs. For the purposes of an international standard, a vulnerable population should be defined as an economically disadvantaged community that lacks adequate access to health care and political power. This definition is broader than

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203. *Supra* notes 13-14 and accompanying text.

204. *Supra* notes 13-14 and accompanying text.

the one in the Guidelines.<sup>205</sup> Central to this recommended definition is the lack of access to adequate health care. Within this definition of a vulnerable population there should be subcategories for those who are legally or otherwise incompetent or unable to provide the necessary consent and the appropriate measures of protection for these groups.

The specific requirements regarding vulnerable populations should expand beyond the reasonable access approach of the Guidelines and recognize other benefits of research as identified by the 2001 Conference on Ethical Aspects of Research in Developing Countries.<sup>206</sup> These benefits include the training of health care or research personnel, construction of health care facilities and other physical infrastructure, and provision of public health measures.<sup>207</sup> The international standard should involve consulting with the particular community to determine what would best benefit the population.

Acknowledging that there may be feasibility issues attached to an improved and enforceable international standard, there are other efforts that could improve current practices. The ICCPR, the only enforceable international standard, should be amended to expand on its basic "free consent" requirement.<sup>208</sup> Article 7 could be amended to provide populations with the right to benefit from experiments in which they participate. There should also be domestic efforts at improved regulation. Any company seeking to market a new drug must secure FDA approval.<sup>209</sup> The FDA should, as part of its approval process, require notification of whether the tested human subjects comprise a vulnerable population. If so, the FDA should then require documentation concerning how the researchers intend to confer benefits on the population. The FDA should create a list of accepted benefits, ranging from the improvement of a health care infrastructure (physical improvement or otherwise), to the provision of the Phase III drugs (if applicable/successful), to the provision of other public health services.<sup>210</sup>

Additionally, medical literature is capable of improving international testing practices. Selected medical journals already require pharmaceutical companies to

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205. The commentary on Guideline 13 defines vulnerable persons as "those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests." *Guidelines*, *supra* note 73 at 64.

206. *Fair Benefits*, *supra* note 3, at 2133-34.

207. *Id.* at 2134.

208. *See ICCPR*, *supra* note 69, at 175.

209. 21 C.F.R. §§ 314-314.65 (2005).

210. The FDA is not the only government body that can adopt such policies. NIH, although it is not a regulatory agency, does provide federal grants to researchers in academic and medical research centers for scientific purposes. *See* <http://www.nih.gov/about/budget.htm>. NIH could require that grant recipients conducting medical research on vulnerable populations demonstrate how they will confer benefits to the community. *See* NAT'L INSTITUTES OF HEALTH, NIH BUDGET, <http://www.nih.gov/about/budget.htm>.

register clinical trials for their reports to be considered for publication.<sup>211</sup> Furthermore, publications such as the *Journal of the American Medical Association* (JAMA) require disclosure and reporting of authors' financial conflicts of interest.<sup>212</sup> Similarly, medical journals should require disclosure and report on the benefits researchers provide to vulnerable communities.

#### CONCLUSION

The current standards guiding human experimentation in developing countries are not preventing the exploitation of vulnerable populations. The Code and the Declaration are too one-sided to be effective. The Guidelines do not fully contemplate or consider the range of vulnerable populations. None of the standards address the various tangible benefits that researchers could be required to supply to vulnerable populations. An improved international standard must consider these elements and effectively balance the various interests involved. This standard would improve upon the current Guidelines by requiring appropriate recognition of vulnerable populations and specific benefits to be bestowed upon the tested population. Benefits should no longer be limited to successful Phase III trials, but rather should encompass a range of possibilities. Assuring that benefits accrue to the vulnerable population will help ensure that the power equation is balanced, with both sides profiting from medical progress.

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211. Howard L. Dorfman & Linda Pissott Reig, *Avoiding Legal and Ethical Pitfalls of Industry-Sponsored Research: The Co-Existence of Research, Scholarship, and Marketing in the Pharmaceutical Industry*, 59 FOOD & DRUG L.J. 595, 601 (2004).

212. *Id.* at 609.