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PROTECTING A VULNERABLE POPULATION WITH LITTLE REGULATORY FRAMEWORK: A COMPARATIVE ANALYSIS OF INTERNATIONAL GUIDELINES FOR PEDIATRIC RESEARCH ETHICS

Heather L. Mullins-Owens, J.D., Macey L. Henderson, J.D., and Jason Henderson, D.O., J.D.*

Research ethics guidelines in developing nations are a topic of great importance to a multi-disciplinary audience, and much has been written about these guidelines from clinical, legal, and ethical perspectives. However, there is little literature which provides international guidelines for vulnerable populations such as children and adolescents. Oftentimes, there are no clear, concise guidelines for inclusion of children and adolescents in research, and guidelines must be assumed or gleaned from normative ethics and theories in the form of principles. This Note will begin with an overview of research ethics rules and regulations as utilized in the United States, followed by an introduction to three primary concepts in pediatric research ethics: the assent process for children, placebo use, and defining minimal risk. After a general introduction to these concepts, we will explore practical applications of these themes within an international framework. China, Kenya, and India, will serve as examples of how pediatric research in developing nations is lightly directed by regulatory guidelines and how research is impacted by local culture.

I. INTRODUCTION TO U.S. BIOMEDICAL RESEARCH REGULATIONS AND GUIDELINES

Throughout the majority of U.S. history, children were widely involved in medical research. Researchers often used their own children in research, solicited orphans, or used the children of servants or slaves.¹ After the publication of Henry K. Beecher’s seminal article in 1966 titled “Ethics and Clinical Research,”² medical research involving children was strongly

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* We also thank Christine Sego Caldwell, who assisted with editing the citations.


discouraged in an attempt to protect children from harm. While the Nuremberg Principles of Research Ethics had been available for nearly two decades, most researchers did not find them readily applicable or relevant to the medical research being conducted in U.S. institutions. The sentiments expressed in the Beecher article eventually led to medical research regulations governing inclusion of children in research in the 1970s.

Since the 1990s, however, there has been growing concern that these regulations restrict children’s participation in research resulting in “therapeutic orphans” (a term coined by Harry C. Shirkey, referring to the lack of studies exhibiting the safety, dosing, and efficacy for drugs used routinely in pediatric populations which were approved only for adults). Eventually, it became evident that excluding children from medical research inhibited their future access to innovative improvements in care and treatments. As such, medical researchers and pharmaceutical companies in the United States and European Union have been strongly encouraged to increase the number of pharmaceutical trials open to children. Participation by children in these countries is viewed more as a right to access ethical medical trials, rather than a need to protect children from research. It is estimated that 75% of drugs prescribed to children lack “adequate testing in children.” With so many drugs not adequately tested for safety and effectiveness in children, determining the appropriate dosing for minors is reduced to educated guesswork.

More clinical studies are being conducted in new regions to achieve recruitment targets and address the highly competitive search for patients in conventional territories such as the United States and Western Europe. There has been a significant increase in the number of pediatric studies conducted in these nonconventional regions, such as the People’s Republic


6. Id.

Kenya has also become a key market for pharmaceutical research, including the development of drugs to treat HIV and AIDS.

Given the growth of the research market in these countries, it is important for medical professionals, ethicists, and health policy analysts to understand the particular challenges of conducting research on children in these markets, and for collaborative relationships and practices to develop in these markets. Collaboration has already begun among some of the traditional markets, such as the U.S., Japan, and Europe, through collaborative institutional relationships and practices.

II. INFORMED CONSENT AND ASSENT PRACTICES AND REGULATIONS IN THE UNITED STATES

The Belmont Report was created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979 and requires that research involving human subjects provide respect for persons. This principle requires two important moral requirements: acknowledgement of autonomy when it exists and the protection of the subject when autonomy is diminished. To respect subject autonomy, the subject must be provided with all relevant information about the risks, potential benefits, and requirements for participation in the research. This process of obtaining informed consent has been defined as an "interactive process between subject and researcher involving disclosure, discussion, and a complete understanding of a proposed research activity, which culminates in the individual freely expressing a wish to participate." In the United States, informed consent has its roots in Schloendorff v. Society of New York Hospital (1914), in which a patient sued her doctor for performing an

8. Id.


Unauthorized surgical procedure. In the decision, Justice Benjamin Cardozo wrote that:

Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages... This is true, except in cases of emergency where the patient is unconscious, and where it is necessary to operate before consent can be obtained.

Additional cases and historical events followed, which reinforced the idea that doctors must disclose all relevant information for patients to make informed decisions and must obtain permission from the patient before proceeding with treatment or research.

In the United States, only a fully autonomous person can give consent. Therefore, minors cannot legally provide consent, and informed consent to participate in research must be sought from the minor's parents or guardians. This parental consent amounts to mere permission, since it grants the researcher permission to request the child's participation in the research.

Assent may be defined as "a child's informed agreement to the conditions of participation." There is less consistency in how, when, and from whom assent is obtained in U.S. research studies because federal regulations leave many of the decisions up to the local Institutional Review Boards (IRBs). Differing age requirements for assent are common, but generally children

13. Id.
15. 45 C.F.R. § 46.402 (2009); Meaux & Bell, supra note 11, at 243.
16. 45 C.F.R. § 46.408.
17. Meaux & Bell, supra note 11, at 243-44; Barbara Conrad & Sharon Homer, Issues in Pediatric Research: Safeguarding the Children, 2 J. FOR SPECIALISTS IN PEDIATRIC NURSING 163, 164 (1997).
seven\(^1\) or older are asked to assent. Minors of this age typically have the capacity to understand (albeit often in non-scientific terms) what type of procedure they will undergo, and how it may differ from the care they would receive if they were not involved in research.\(^2\) For a child’s assent to be valid, all information about the research must be disclosed in developmentally appropriate and comprehensible language to the child.\(^3\) A child’s dissent to participate supersedes a parent’s consent to research participation.\(^4\) Assent by children is typically affected by two types of factors: individual factors, such as age, developmental level, and health status; and environmental factors, such as role constraints, family factors, differences in education between investigators and community members, access to non-research related health services, and consent-seeker factors.\(^5\)

It should be noted, however, that this focus on autonomy is based on a western concept of personhood,\(^6\) which has its origins in the work of Western philosophers, such as Emmanuel Kant, who said that “all rational beings have the capacity to act in a consistent moral manner and they should be allowed to do so.”\(^7\) This point that everyone has a right to make their own decisions and that these decisions are to be protected and respected by others, was central to the Belmont Report, and remains central to the contemporary U.S. notions of autonomy and informed consent.\(^8\)


\(^{21}\) Meaux & Bell, supra note 11, at 243-44.

\(^{22}\) Id.

\(^{23}\) Id. at 244.


\(^{26}\) Id.
III. PLACEBO USE

Medical practice in children is quite different than in adults. While most studies are performed using adult populations, adult populations require different doses of medication, lengthier follow-ups, and the risk of long-term adverse events during development and sexual maturity.\(^\text{27}\) The efficacy of a drug in children is usually extrapolated from studies in adults, but not the safety and dosage.\(^\text{28}\) Thus, age of the child and the parents’ demand for the best therapeutic options for their child create special obstacles for exercising the ethical principle of autonomy.\(^\text{29}\) The use of placebos in controlled trials has been and continues to be controversial. The 2008 version of the Declaration of Helsinki restricts use of placebo trials to those where there is no current treatment and there is sound rationale for its use.\(^\text{30}\) In such cases, the patient receiving a placebo, or even no treatment, should not be subject to risk or harm.\(^\text{31}\) Placebos may also be used when they are methodologically necessary to determine the efficacy of an intervention.\(^\text{32}\)

Ethical Guidelines of the Council for International Organizations of Medical Sciences (CIOMS) proffered specific guidelines for the use of placebos in pediatric populations: (1) When there is not a commonly-accepted treatment for the condition and the medication under study is the only medication that can modify the course of the disease’s progression; (2) When the commonly-used treatment for the condition is of questionable efficacy; (3) When the commonly-used treatment for the condition has undesirable side effects and the risks of use can be significantly greater than the benefits; (4) When the placebo is used to identify the incidence and severity of undesirable side effects produced (when adding a new treatment to an established regimen); or (5) When the disease is characterized by an

\(^{27}\) Committee on Drugs, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Population, 95 PEDIATRICS 286, 286 (1995).


\(^{29}\) See Whittle, et al., supra note 20.


\(^{32}\) Puri et al., supra note 30, at 133.
increase in frequency, exacerbations or spontaneous remission and the efficacy of the treatment has not been proven. 33

Federal regulations in the United States provide no reference to the use of placebos in pediatric populations, so the CIOMS guidelines for placebo use are firmly recognized as guiding authority. 34 It has been suggested that each intervention, placebo, and drug should be assessed for a risk-benefit profile both separately and collectively. 35 Without much specific guidance on what constitutes certain risk profiles, ethical placebo-controlled, pediatric trials will have to comply with both the above-mentioned placebo intervention and the drug intervention guidelines. 36

IV. DEFINING MINIMAL RISK IN PEDIATRIC RESEARCH

How is minimal risk defined in pediatric research in the United States? The Code of Federal Regulations (C.F.R.) defines minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 37 In 2002, The Institute of Medicine called for a more risk-based review process so that studies posing "minimal risk" "should be handled diligently, but expeditiously, while studies involving high risk should receive the extra time and attention they require." 38

The United States federal regulations do not further specify the risks of daily life. Nor do they define what constitutes a "direct" benefit or a "minor increase" over minimal risk. 39 Accordingly, whether children are enrolled in


34. Paula L. Knudson, Ethical Issues in Human Subject Research with Children, 33 ARCH. MED. RES. 203, 203 (2002).


36. Id. at 106.

37. 45 C.F.R. § 46.102(i) (2009).


39. 45 C.F.R. § 46.102(i).
clinical research only when the risks are low, and whether the clinical research offers the potential for individual benefit, depends on how a particular Institutional Review Board (IRB) applies the federal risk and benefit categories. When assessing whether research participation offers the pediatric patient a sufficient individual benefit to justify the risks, the federal regulations direct IRBs to consider only "direct" benefits to pediatric participants. The IRB guidebook notes, however, that "[d]irect payments or other forms of remuneration offered to potential subjects as an incentive or reward for participation should not be considered a 'benefit' to be gained from research." To minimize the potential for exploitation in research, the "minimal" risk standard should be interpreted as referring to risks in daily lives of "typical" children; minimal risk should be defined as the probability and magnitude of harms that are normally encountered in the daily life of the general population.

V. CHINESE REGULATIONS BACKGROUND FOR HUMAN SUBJECTS RESEARCH

A. Overview of the Regulations and Guidelines for Ethical Human Subjects Research

The Chinese bioethics landscape offers a rapidly developing and sometimes overlapping array of regulations and guidelines to be followed over clinical research. As research funding from the Chinese government increased in the past decade, the requirement for ethical review of protocols increased as well. The development of China's State Food and Drug Administration (SFDA) in 2003 helped harmonize varying clinical research


41. Id. at 477.

42. OFFICE FOR THE PROT. FROM RESEARCH RISKS, PROTECTING HUMAN RESEARCH SUBJECTS: INSTITUTIONAL REVIEW BOARD GUIDEBOOK 3-8 (1993).


44. Id.

It also increased transparency in the drug approval process. In its inaugural year, the SFDA issued Good Clinical Practice (GCP) standards, which clearly defined Contract Research Organizations (CROs) and stipulated that CROs could conduct clinical trials for their clients. Finally, in 2007, the Ministry of Health (MOH) enacted Regulations on Ethical Reviews of Biomedical Research Involving Humans, ("2007 Regulations").

Ethical review of all human subjects trials in China are required to comply with the principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) Guidelines, according to Clinical Drug Trial Guidelines. Chinese law additionally requires that investigators comply with all Good Laboratory Practice (GLP) and GCP Guidelines in all pre-clinical and clinical drug trials. GCP governs clinical trials in China and the regulation provides more specific procedural requirements than the other Chinese regulations considered here.

This principle-based framework has been criticized for possible ethical imperialism because the focus on individual autonomy seems at odds with a culture which has emphasized social harmony over individual autonomy for centuries. China is not alone, as many developing countries have virtue-based ethics. This focus on relationships is also seen in Western concepts of feminist bioethics.

The Chinese MOH is primarily responsible for providing ethical guidelines for research involving human subjects. The Chinese Academy of

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47. Id.


50. Id. at 12.

51. Wang & Henderson, supra note 45, at 1867.

52. Id.
Medical Sciences (CAMS) and China Center for Disease Control and Prevention (CDC) operate under the MOH, which also funds bioethics research. The SFDA has also been under MOH control since 2008 (a change of policy to create more governance of the agency after a 2007 scandal involving the director, Zheng Xiaoyu, who was arrested and executed on corruption charges). Since moving under SFDA control, the agency has been given increasingly positive press for establishing more supervision of its policies and leadership, and seems to have “radically reformed.”

B. Ethical Review of Research in China

China has followed the U.S. model of IRBs, referred to in China as Ethics Committees (ECs), which makes the process of approving clinical trials similar to the process in the United States. The SFDA has roughly 40,000 employees, and is responsible for food safety and regulation, medicinal product and medical device regulations. All proposed clinical trials are reviewed by the SFDA, and trials must be conducted at a certified center. China has approximately 160 certified centers, open to random inspections by the SFDA. Similar to the IRBs in the United States, the ECs review clinical trials, and can approve, deny, or require modifications of the presented proposals. The ECs are required by the 2007 Regulations to include at least five people for five-year renewable terms. The SFDA Clinical Drug Trial Guidelines require the ECs to include male and female non-medical members and members of independent institutions, all of whom will independently review the research.

53. CURE COMMITTEE REPORT, supra note 49, at 25
54. Id. at 32.
55. Id. at 24.
56. Id.
57. Id.
58. Id.
59. Id. at app. 1, at 48.
60. Id. at app. 1, at 44.
The China-UK Research Ethics (CURE) Committee Report noted that the quality of ECs in China varied in comparability to U.S. institutions, with the ECs in Beijing and Shanghai offering the highest overall protections to human subjects, while some institutions in smaller municipalities lagged behind. Generally, institutions that ranked highly in their fields also had the highest standards for selecting ECs. International accreditation has already been granted to many hospitals throughout China for their culture of patient safety. The Joint Commission International (JCI) lends accreditation to the entire hospital, and the College of American Pathologists lends accreditation to laboratories.

C. Pediatric Research

Following the European and United States encouragement of pediatric pharmaceutical research in the late 1990s, the 2003 Good Clinical Practice (GCP) Guidelines permitted drug manufacturers to enroll children in closely monitored clinical drug trials. Article XIV (F) of the 2007 Biomedical

61. Id. at 15.

62. See id at 17.

63. Chinese Hospitals with full hospital-wide accreditation include: Beijing United Family Hospital and Clinics, Beijing; Clifford Hospital, Guangzhou, Guangdong Province; HOME Women’s and Children’s Hospital (Shenzhen), Shenzhen City, Guangdong Province; Huashan Hospital, Fudan University, Shanghai; Jian Gong Hospital (Health Palace Hospital), Beijing; Luoyang Orthopedic-Traumatological Hospital of Henan Province, Luoyang, Henan Province; NJ HSCB Obstetrics and Gynecology Hospital, Nanjing, Jiangsu Province; Shanghai Children’s Medical Center, Shanghai; Shanghai United Family Hospital and Clinics, Shanghai; QingHai Red Cross Hospital, XiNing, QingHai; Sir Run Run Shaw Hospital, Hangzhou Zhejiang Province; TEDA International Cardiovascular Hospital, TEDA, Tianjin; Tianjin Ninghe Hospital, Tianjin City; Yanhua Hospital, and Beijing; Zhengzhou People’s Hospital, Zhengzhou, Henan Province. JCI Accredited Organizations, JOINT COMM’N INTERNATIONAL, http://www.jointcommissioninternational.org/JCI-Accredited-Organizations/ (filter “Country” drop down for “China”).

64. The JCI accreditation process is designed to “create a culture of safety and quality within an organization that strives to continually improve patient care processes and results.” JOINT COMM’N INTERNATIONAL, http://www.jointcommissioninternational.org (last visited Jul. 17, 2012).

Research Involving Human Ethics Review Principles states that children, pregnant women, the mentally handicapped, mental patients, prisoners, poor, and less educated persons should be given ‘special protections’ by the reviewing ethics committees.

The 1998 Interim Regulation for Ethical Review of Biomedical Research Involving Human Subjects (“Interim Regulation”) in China requires written informed consent from competent human subjects in advance of biomedical research. Article 9 of the Interim Regulation bars children from participation in the same research as adults without written consent from the parent or guardian of each child; however, the child’s choice to not participate in research invalidates parental consent. Possible harm or risk to children must also be minimized, and therapeutic research efficacy shall not be lower than existing therapies.

D. Factors to Consider When Evaluating the Impact of Chinese Research

Although there are 400 million children in China, the country is home to only 60,000 pediatricians and only four pediatric pharmacologists. This number is alarming, particularly since the number of pediatric trials being conducted in China is rising each year. China also lacks clear sanctions for violating ethical regulations governing human research. Moreover, the research-conducting institutions are largely responsible for monitoring and self-enforcing adherence to guidelines and regulations. Due to these factors, research conducted in China may be held to varying levels of ethical safeguards. One of the key issues frequently brought up in literature

66. CURE COMMITTEE REPORT, supra note 49, at app. 1, at 48.
67. Id.
68. Id.
69. Id.
70. Li & Wang, supra note 65, at 16.
71. CURE COMMITTEE REPORT, supra note 49, at 31.
72. Id. at 8.
73. Id.
74. Id. at 23.
regarding ethical regulations of Chinese medical treatment is the approach to
c Familial decision making and the effect it has on how informed consent is
obtained in medical research and treatment, which we will later explore in
greater detail.75

Although the number of clinical trials in China is not yet on par with the
United States or Europe, it continues to increase significantly each year.76
In 2008, the contract research organization (CRO) market was estimated to
be worth $250 million.77 The market value of CROs in China was $2.6
billion in 2010.78 Those numbers are even more impressive considering that
the CRO market in China only developed in the 1990’s.79 China offers
readily accessible human subjects, principal investigators with extensive
experience with Western pharmaceutical companies,80 and the costs of
developing a drug in China are only 20% of the costs to develop one in the
United States.81 Furthermore, China is a very large potential consumer
market, because China is home to approximately 1.5 billion people, or
roughly one-fifth of the world’s population.

According to Dennis Gillings, CEO of Quintiles Transnational, while the
United States and Europe continue to dominate contract research (with 88% of
the global market as of 2006), growth in the share of Chinese market
value is anticipated to grow to many times beyond its current share by

75. Wang & Henderson, supra note 45, at 1876; see also Daniel Fu-Chang Tsai,
How Should Doctors Approach Patients?: A Confucian Reflection on Personhood, 27 J.
MED. ETHICS 44, 48 (2001), available at http://jme.bmj.com/content/27/1/44.full.pdf+
html [hereinafter A Confucian Reflection on Personhood].

76. JENNIFER ZAINO, WIPRO, THE STATE OF GLOBAL CLINICAL RESEARCH TRIALS

77. Hayduk et al., supra note 46, at 8.

2011/08/18/NE54360.

79. Hayduk et al., supra note 46, at 8.

80. Id.

Pharma Sector, PHARMAMANUFACTURING.COM, http://www.pharmamansufacturing.com/
Growing numbers of global pharmaceutical companies are establishing research and development centers in China, including Novo Nordisk, AstraZeneca, Eli Lilly, Roche, and Pfizer.

E. Tension Between Imported Guidelines and Domestic Culture

Various guidelines for human subjects protection in research are superficially quite similar to those in the United States, but substantial cultural differences should be taken into account when considering how research should be conducted in China. The most striking of these cultural differences related to health care may be the practice of familial consent. Individual informed consent is required in all clinical trials in China in the same manner it is in the United States, but in China, consent of the family and sometimes even the community is often also sought, at least in clinical matters. In the United States, standards for clinical research focus on the beneficence, autonomy, non-maleficence, and justice principles, with liberty and rights of the individual as a central focus of ethical considerations and decision making. Conversely, Chinese culture has been strongly influenced by Confucian philosophy since the Han dynasty (206 BC–220 AD). In fact, the Chinese had a written code of medical ethics as early as the 7th century, written by Sun Szu-miao. This code identified “three classical Chinese virtues: humanness, compassion, and filial piety.”

82. Id.

83. Id.


86. See generally Cheng-tek Tai & Lin, supra note 25, at 52.

87. Id.

88. Id. at 51.
Confucians may view autonomy to be just as important as Western bioethicists; however, autonomy is viewed as “collective rather than individualistic.”

Confucian tradition views a community as starting with the family unit, rather than the individual, and therefore autonomy may be seen as a “collective right rather than individual privilege.”

Confucianism has provided the primary Chinese social, moral, political, and educational philosophy for centuries, including the framework for China’s longstanding tradition of mediation rather than litigation. Confucius’s idea of “persons” was “best interpreted via his theories of ‘chun-tze,’ (the morally ideal person), encapsulating a two-dimensional approach, (the ‘autonomous person’ and the ‘rational person.’).”

A “Confucius understanding of personhood encompasses the western concepts of free will and rationality, which provide strong support for informed consent techniques,” but “Confucian concepts of personhood are balanced with a strong relational perspective or ‘horizontal dimension’ with specific responsibilities to others.”

As recently as 1955, Tsai reminds us, Szasz and Hollender proposed models of physician-patient relationships based on different levels of capacity in decision making: the activity-passivity model (similar to parent-infant communication); the guidance-cooperation model (similar to a parent-adolescent child communication); and the mutual participation model (similar to an adult-adult communication). These were later replaced by models such as the one proposed by Beauchamp and Childress which put a stronger focus on autonomous decision making.

When a doctor approaches his patient, he sees a person not only as a moral agent with autonomy and dignity to be respected, namely, the patient’s concerns, preferences and choices to be respected and

89. Id. at 52.

90. Id.

91. A Confucian Reflection on Personhood, supra note 75, at 44.

92. Olsen, Wang, & Pang, supra note 24, at 180 (emphasis added).

93. See T. S. Szasz & M. H. Hollender, A Contribution to the Philosophy of Medicine, 97 ARCH. INTERNAL MED. 585 (1956).

94. Id. at 590.

95. See generally BEAUCHAMP & CHILDRESS, supra note 85.
his rights protected. He also sees the patient as a relational being with certain family, community and social-historical contexts: a small self-encompassed by one or many greater selves. In a Confucian context, the family, more than the individual, is often considered as one basic unit in the two aspects of doctor-patient relationships. Medical ethical decision-making tends to respect the opinions and decisions made or agreed to by the family as a whole. Given the concept of relational personhood, the emphasis on family values, the large role and responsibility family usually take in caring for sick persons, and the interconnectedness and interdependence between family members, families must be taken seriously.96

While many of the ethical questions related to personhood and autonomy interpretations in China arose out of clinical care rather than research, the principles of autonomy related to research are similar. In fact, the ethical issues may be even more pressing in terms of research subjects. Most subjects will have time to solicit consent/assent from their families prior to consenting, since research-related decisions are typically not as urgent as clinical care decisions. Multiple federal guidelines are in place in China which collectively represent a more Western approach to autonomous individual consent in clinical research.97 However, in reference to research, it is unlikely that the process of gathering consent is completely void of any influence of traditional Confucian familial cultural norms.

Much of the Chinese bioethics literature on the topic of familial assent/consent refers to the culturally appropriate balance of seeking to obtain individual consent and familial assent.98 Familial assent is particularly important when dealing with rural and less educated Chinese communities. It should be noted that this extra procedural step of familial assent, when used with individual consent of the participant, may not always be viewed in a negative light when conducting collaborative research. The World Health Organization (WHO), in its Research Ethics Review Committee (ERC) Information for Researchers Concerning Informed Decision Making, Section IV, endorsed familial assent. However, one cannot gloss over the impact this may have on pediatric and adolescent care

96. A Confucian Reflection on Personhood, supra note 75, at 48.

97. See generally Clinical Trials in China, RJS MEDICAL TECHNOLOGY INC. http://www.sfdachina.com/info/91-1.htm (last visited Nov. 12, 2012); see also CURE COMMITTEE REPORT, supra note 49.

98. See sources cite, supra note 84.
and research, including the increased probability that a child will be persuaded by the family.

F. Enforcement of Chinese Research Guidelines and Ramifications for Noncompliance

The specific substantive protections embodied in 45 C.F.R. § 46 are also embodied in the 2007 Regulations promulgated by the MOH. The 2007 Regulations state that violations by individuals or institutions will be punished. These punishments vary but include “open criticism,” withdrawal or termination of positions, and withdrawal or termination of qualifications to perform professional work. These punitive measures fall short of the more severe punishments under U.S. law, which may include criminal charges.

G. Improving Evidence Based Medicine and Research in China

Uneven regional development is one of the challenges to improving evidence-based medicine and research in China. In Beijing and Shanghai, for example, researchers can search medical literature for free at their university using popular international databases. Physicians in more remote locations, however, may be inhibited by a lack of available resources and a more limited knowledge of English, possibly preventing the use of the best evidence in their research or clinical care. An additional problem for Chinese researchers is that major medical journals lack clinical evidence originating in China. In a recent article by Jiyao Wang, the author states:

from 1999 to 2008, 1880 clinical research articles were published in The New England Journal of Medicine, The Lancet, and JAMA. However, only 0.21% of these were from mainland China. Wu and colleagues analyzed randomized trials on 20 common diseases published in China’s natural knowledge infrastructure

99. CURE COMMITTEE REPORT, supra note 49.


101. Id.

102. Id.

103. Id. (citing T. Wu, Y. Li, Z. Bian, G. Liu & D. Moher, Randomized Trials Published in Some Chinese Journals: How Many are Randomized?, 10 TRIALS 46 (2009)).
database from 1994 to 2005, and found that only 7% of them met methodological criteria (according to Cochrane review criteria). Frequent errors in statistical analyses are also found in Chinese medical journals, which reduces the credibility of the evidence.104

There is also credible evidence that improving the quality of local medical research, as well as publishing the research, would improve best clinical practices in many remote areas in China and beyond, as uncovered by a recent survey involving China, India, and Kenya.105 A PubMed search for clinical research articles from 2000-2009 from China, published nationally or internationally, found that published articles regarding clinical research from China increased an average of 22% per year.106 Additionally, most well-run clinical trials are pharmaceutical pre-marketing trials due to a lack of other funding for randomized trials.107 Wang appropriately suggests that so many sponsored trials could result in publication bias for those products.108

H. Evaluating Chinese Research Regulations

The remarkable similarities between Chinese and U.S. regulations for research involving human subjects and children provide an adequate basis for collaborative and contracted research between the United States and China if strict enforcement of these guidelines can be assured. It is clear that the primary principles of "ethical" research and informed consent practices are present in both systems, although consent is traditionally interpreted differently by country. The explosive growth in the CRO market in China also raises concerns that enforcement of guidelines may not be developing quickly enough to protect human subjects in some regions.

We believe the societal focus on the family in China's practice of obtaining consent and assent reflects Chinese society the same way the individual-centric focus of U.S. regulations for consent and assent reflect American society. Because no two societies are identical, as Emanuel

104. Id.


107. Wang, supra note 100, at 532.

108. Id.
pointed out in *The Benchmarks of Ethical Research*, "differences in . . . social traditions and practices make the process of informed consent in developing countries complex." 109 Understanding the cultural context in which decisions are traditionally made will better ensure that ethics regulations will be both protective of subjects and culturally sensitive to the populations those regulations are intended to serve.

VI. INTRODUCTION TO REGULATIONS IN KENYA

The National Council for Science and Technology (NCST) is responsible for coordinating all research in Kenya and advising the government on research-related matters. NCST also makes final decisions about protocol applications in Kenya. 110 Two other national bodies involved in ethical review are the Kenya HIV/AIDS Vaccine Subcommittee and the Pharmacy and Poisons Board, both of which are affiliated with the MOH. 111 Through this government oversight, Kenya developed three fundamental documents promulgating human subjects research guidelines. First, NCST promulgated *Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya*, pursuant to the Science and Technology Act of 1979. 112 These guidelines set forth a framework for determining if a research proposal is ethical with respect to the following factors: value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent and respect for potential and enrolled subjects. 113

Second, the Kenya Medical Research Institute (KEMRI) has guidelines for research that will be conducted through that institution. KEMRI was established as an Amendment under the 1979 Science and Technology Act

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110. NAT'L COUNCIL FOR SCI. AND TECH., NCST No. 45, GUIDELINES FOR ETHICAL CONDUCT OF BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS IN KENYA 2, 3, 10 (2004) (Kenya) [hereinafter GUIDELINES FOR ETHICAL BIOMEDICAL RESEARCH]; see also Science and Technology Act of 1980, ch. 250 art. 3-5 (Kenya).


112. GUIDELINES FOR ETHICAL BIOMEDICAL RESEARCH, supra note 110.

113. *Id.* at 2-9.
to be a national body responsible for implementing health science research.\textsuperscript{114}

Third, in 2005, the MOH enacted \textit{National Guidelines for Research and Development of HIV/AIDS Vaccines}. These guidelines specifically address human subjects research proposals relating to the effort to identify HIV/AIDS vaccines.\textsuperscript{115}

\textbf{A. The Applied Process of Ethical Review in Kenya}

Kenya has a multi-tiered review system for human subjects research. Research proposals must generally go through two to three reviews before approval.\textsuperscript{116} Depending upon local requirements, some proposals must first be reviewed by the researcher’s department within the local institution.\textsuperscript{117} Then the ethical review committee at the host institution where a local researcher is based or where a foreign researcher is collaborating must review the proposal.\textsuperscript{118} Once this review is completed, a review is performed by the NCST.\textsuperscript{119} Researchers not affiliated with a specific institution or affiliated with an institution that lacks an ethical review committee petition directly to NCST for review.\textsuperscript{120}

While researchers typically must seek final approval from NCST, certain institutions have final approval power themselves. KEMRI and Kenyatta National Hospital maintain committees with final approval power.\textsuperscript{121} These

\begin{itemize}
\item \textsuperscript{114} \textit{Science and Technology Act}, supra note 110.
\item \textsuperscript{115} \textit{KENYA NATIONAL GUIDELINES FOR RESEARCH AND DEVELOPMENT OF HIV/AIDS VACCINES}, supra note 111, at 23-27.
\item \textsuperscript{116} \textit{GUIDELINES FOR ETHICAL BIOMEDICAL RESEARCH}, supra note 110, at 2, 3, 10.
\item \textsuperscript{117} \textit{Id.}
\item \textsuperscript{118} \textit{Id.}
\item \textsuperscript{119} \textit{Id.}
\item \textsuperscript{120} E-mail from Pauline Mwinzi to David Borasky (Feb. 6, 2006) (on file with author); E-mail from Pauline Mwinzi to Kelly Safreed Harmon (Feb. 21, 2006) (on file with author).
\item \textsuperscript{121} C. S. Molyneux et al., ‘Even if they ask you to stand by a tree all day, you will have to do it (laughter). . . !’: Community Voices on the Notion and Practice of Informed Consent for Biomedical Research in Developing Countries, 61 SOC. SCI. & MED. 443, 444–45, 450 (2005).
\end{itemize}
hospital ethical review committees are responsible for reviewing all research proposals from MOH researchers.\footnote{122} For HIV/AIDS vaccine research, investigators must submit a concept paper to the Kenya HIV/AIDS Vaccine Subcommittee seeking approval.\footnote{123} The investigators must next submit a proposal simultaneously to the Pharmacy and Poisons Board and to NCST or another designated ethical review committee. Both of those bodies must approve the research plan.\footnote{124} Enforcement of these stipulations is always a concern, especially as it relates to ethical research considerations in pediatrics. All three of the guidelines described above are legally binding and enforceable, as they have been promulgated through acts of Parliament.\footnote{125} In addition, KEMRI has a disciplinary committee to ensure that the agency’s research complies with all relevant requirements.\footnote{126}

\textbf{B. The Issue of International Pediatric Research Ethics Guidelines}

Since the vast majority of clinical research pertaining to children in Kenya is in collaboration with international sources, issues often arise due to differing viewpoints regarding appropriate ethical and procedural issues. As discussed above, current Kenyan research guidelines are not in alignment with many international jurisdictions, including the United States, United Kingdom, and Europe. This raises several pertinent questions for any researcher involved in international research, including: how should consensus be reached when clear consensus may not be present within a single country?, and when collaborating partners have different ideas about appropriate ethical standards,—in this case, ethical issues in pediatric research—how should those differences be resolved? To best resolve these issues, a comparison of ethical issues surrounding pediatric research will be detailed, first with the state of pediatric research in the United States, followed by a review of the state of pediatric research in Kenya.

\footnote{122} Id.

\footnote{123} Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines, \textit{supra} note 111.

\footnote{124} Id.

\footnote{125} Guidelines for Ethical Biomedical Research, \textit{supra} note 110, at 2, 3, 10.

C. Current State of Pediatric Research Ethics in Kenya

Kenya is a developing country undergoing a major health crisis primarily due to a combination of extreme poverty, poor sanitation, and high rates of HIV/AIDS infection. As such, Kenya has not enjoyed the innate wealth and scientific ability necessary to be on the forefront of full legislative protection of children in research initiatives. Nonetheless, one key issue pertaining to research ethics and children in Kenya is proper informed consent. Studies have clearly defined this problem, one of which is multi-factorial in etiology. In a qualitative study examining opinions of Kenyan community members related to informed consent for research, Molyneux et al. asked community focus groups whether consent should be sought from Kenyan children from whom blood samples would be requested. They reported that all of the groups “reacted with surprise” to the question of considering consent for children, with “general agreement that children should not be asked,” and they further specified that investigators should not consider asking children aged ten to twelve years. The study participants reported concerns that the children could not “reason things out” or understand why samples were needed, and they felt that fear of pain would be the children’s only consideration. Even for children aged ten to thirteen years, the Kenyan community members felt that researchers should discuss the project directly only with the parents, and then the parents could relay the information to the children. The practice of deferring consent to the parents does not align with the Kenyan government’s position.

The Guidelines for the Ethical Conduct of Biomedical Research Involving Human Subjects published by the Kenya NCST support respect for the dissent of pediatric research subjects, stating that when “the child refuses to participate in the research, that refusal must be respected unless there’s no other medical alternative from which the child could benefit.” While these guidelines do not specifically mandate pediatric assent, the clear emphasis on respecting a child’s dissent might suggest a similar position.

127. Molyneux et al., supra note 121, at 444-45.
128. Id.
129. Id.
130. Id.
131. GUIDELINES FOR ETHICAL BIOMEDICAL RESEARCH, supra note 110.
132. Id.
These guidelines could also be interpreted as willingness to rely on implied assent, assuming that active dissent was not voiced. The Kenyan government realizes that appropriate pediatric informed consent is a key ethical obligation for clinical studies, but empirical studies show that the key requirements are often not met by community leaders.  

D. The Dilemma – Closing the Apparent Gaps Between the Kenyan Government and Kenyan People in Regards to Ethical Research for the Pediatric Population

The application of voluntary informed consent is one element of ethically sound clinical research. The difficulties of achieving genuine informed consent in practice are widely recognized, particularly where research involves children and in settings where investigators have significantly different educational and socio-cultural backgrounds to study participants, as in Kenya. To address this concern, one must first identify the causes of the problem.

In 2004, the KEMRI examined perceptions, understanding, and appropriateness of informed consent processes for pediatric research in low-income settings of Kenya. While every study and consent form was reviewed in advance by independent national and international committees, the views and understanding of the ‘subjects’ of these activities had never been documented. The principal approach to exploring informed consent (“the consent study”) was the use of three ‘research case studies,’ each of which was a study that had been approved locally, nationally, and internationally and was on-going at the time of the consent study. The findings highlighted a range of inter-related issues for consideration in future study settings and beyond. Some of these issues include conceptual and linguistic barriers to communicating effectively about research, the critical


135. Molyneaux et al., supra note 121.

136. Id. at 444-45, 450.

137. Id.
and complex role of fieldworkers and nurses in consent procedures, features of research unit-community relations which affect these processes, and the special sensitivity to certain issues such as blood sampling. In sum, the data identified in the study suggests that research messages in Kenya are lost in the researcher-communicator-parent chain in both community-based and in-patient studies.

E. Working to Improve Pediatric Research Ethics Guidelines in Kenya

Despite the Kenyan government enacting legislation and recommendations for protection of children in clinical research, other factors, mainly socio-economic in nature, have prevented these recommendations from being fully implemented. This is not uncommon in developing countries, as evolution in research protections are gradual processes. It starts with government implementation and trickles downward thereafter throughout the sovereign. Emanuel et al. have developed a framework for ethical clinical research in developing countries that includes collaborative partnership as a key principle for multinational clinical research. Among the benchmarks for this principle is respect for the community’s values, culture, traditions, and social practices. Based upon these principles, we can address the current problem with ethical research development in Kenya by targeting three inter-related themes: issues relating to the concept and terminology for research, the role of communicators, and the research unit-community power relations.

F. Conceptual and Terminology Issues

Many community members in rural Kenya are not familiar with the concept of research, and there are no commonly used or universally understood terms for “research.” While the absence of more complex research-related terms such as ‘placebo,’ ‘genotyping,’ and ‘randomization’ is regularly referred to in the literature, this more basic point is given less

138. Id.
139. Id.
140. Emanuel et al., supra note 109, at 934.
141. Id.
142. Id.
attention. Informal discussions with researchers suggest that staff are generally not aware of the substantial communication barriers between researchers and laypersons in discussing biomedical research. In practice therefore, the research message can often be lost early in the communication, with the rest of the information, however detailed, not linked to research. These concept and terminology problems may be resolved through improved communicator fluency.

G. The Role of Communicators

Regardless of the wording on consent forms and explanations given to fieldworkers by supervisors, the details disclosed and focused upon by fieldworkers are heavily influenced by other factors such as self-perceived parental interest in the information and the ability to understand it, the fieldworkers' own understanding of the importance of the notion of informed consent, the balance between risk and benefits, and time pressures. Fieldworkers often simplify research-related information from forms, focusing on the practical details and benefits instead, in part because of the above-mentioned complications. Simplification and focusing on benefits make sense: these aspects are easier to explain and are the primary concern of potential participants. Benefits may also be "hyped up" for some studies, or—as one researcher put it—"nuts and bolts" may be added. Much of the ongoing pediatric clinical research in Kenya is of the upmost importance in the lives of children whom may be recruited, because if they are not recruited, they may die. Thus, the study benefits may become the

143. Molyneux et al., supra note 121, at 444–445, 450.
144. Id.
145. Id.
146. Id.
147. Id.
148. Id.
149. Id.
150. Id. In addition to the approximately 91,000 new infections among adults, it is estimated that 12,894 children under age 15 became newly infected with HIV in 2011, with the overwhelming majority contracting the virus during pregnancy or delivery or as a result of breastfeeding. In 2011, an estimated 49,126 people in Kenya died of AIDS-
paramount focus in the fieldworkers’ minds and the justification for attempts to persuade subjects to join and remain in studies. This may, in part, be due to a genuine overlap between clinical and research practice in much clinical research, i.e., most ethical review committees require research benefits outweigh the risks, and from clinician researchers’ own moral and practical perspective—they do.\textsuperscript{151}

While many of these notions may be interpreted negatively, the flipside is that fieldworkers may minimize refusals based on misunderstandings, in biomedical terms, of the associated risks, thereby ensuring that community members do not miss out on study-specific benefits. It is worth mentioning that these behaviors would be supported by many community leaders in Kenya.\textsuperscript{152} While researchers should possess the notion of informed consent, many community members in Kenya (particularly mothers with little formal education) would find it difficult to understand and accept the information.\textsuperscript{153} As such, many researchers feel study details would actually heighten confusion and concerns.\textsuperscript{154}

\textbf{H. Unit-Community Relations}

Many documented comments by fieldworkers and parents in Kenya suggest that feelings of trust, awe, fear, and anxiety play a significant role in decision-making for joining studies, both in the field and in the hospital, and lead to a considerable gap between disclosure and decision making.\textsuperscript{155}

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related causes, due mainly to lack of access of retroviral treatment. The epidemic has resulted in a sharp deterioration of basic health indicators. Between 1998 and 2003 – or roughly between the epidemic’s peak in Kenya and the early introduction of antiretroviral therapy – the adult mortality rate (ages 15–49) rose by 40% for women and by 30% among men. With a large number of newborns newly infected each year, the epidemic has also increased mortality among children under five. See \textsc{National AIDS Control Council (NACC) & National AIDS and STI Control Programme (NASCOP), The Kenya AIDS Epidemic Update 2011} (2012), available at http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/ce_KENarrative_Report.pdf.
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151. Molyneux et al., supra note 121, at 444–445, 450.
152. \textit{Id}.
153. \textit{Id}.
154. \textit{Id}.
155. \textit{Id}.
\end{flushleft}
Regardless of what is actually said by the fieldworkers during the consent process, many parents report that the Unit (or hospital) staff should just do whatever they feel is right, or agree with what is told to them because there may be unknown or unspecified benefits in the future. While the importance of such psychosocial effects in informed-consent processes has been observed in high-income countries,\textsuperscript{156} what make them particularly strong or unique in a low-income setting is the nature of public sector-citizen relations, and the overall perceptions of the role of the institution.

Inequitable doctor-patient relations have been observed in clinical settings all over the world. In high-income countries, an egalitarianism has evolved, partially as a result of an increasingly educated public and the threat of lawsuits. Patients, therefore, ask more questions, are more likely to know their rights, dispute a doctors' authority, and demand answers. In low-income countries, like Kenya, relations in the public sector are more paternalistic: many doctors communicate the least amount of information possible to their patients.\textsuperscript{157} While this may be expected and accepted, the negative health worker behaviors that are so often reported are not.\textsuperscript{158} Such behavior is in large measure the outcome of drastic declines in real terms of public sector salaries, which have led to demoralization, de-motivation, and cynicism in many.\textsuperscript{159}

The perceived influence that the Unit staff has in allowing community members to access such benefits gives them significant power relative to parents and patients.\textsuperscript{160} This is especially the case in the hospital setting, where many parents express powerlessness upon arrival.\textsuperscript{161} This was

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\textsuperscript{157} Marie-Pierre Préziosi et al., Practical Experiences in Obtaining Informed Consent for a Vaccine Trial in Rural Africa, 336 NEW ENG. J. MED. 370, 370 (1997).

\textsuperscript{158} Mary Travis Bassett et al., Professionalism, Patient Satisfaction and Quality of Health Care: Experience During Zimbabwe’s Structural Adjustment Programme, 45 SOC. SCI. & MED. 1845, 1847-48 (1997).

\textsuperscript{159} Malcolm Segall, From Cooperation to Competition in National Health Systems—and Back?: Impact on Professional Ethics and Quality of Care, 15 INT’L J. HEALTH PLANNING & MGMT. 61, 66 (2000).

\textsuperscript{160} Préziosi et al., \textit{supra} note 157, at 370.

\textsuperscript{161} \textit{Id.}
\end{flushleft}
usually described as a relief: mothers had carried out a range of therapeutic options before coming and undergone significant trouble and cost to reach the hospital.\textsuperscript{162} Responsibility for the child was then handed over to experts who were trusted to do whatever they could.\textsuperscript{163} These situations, previously positive experiences of the hospital, or the Unit’s reputation for handling severely sick children, contribute to relatively strong feelings of trust and awe in staff–community interactions.\textsuperscript{164}

Pediatric research guidelines in Kenya clearly demonstrate a common ethical conundrum highly prevalent in global health research: the lack of consistency in applying ethically permissible informed consent.\textsuperscript{165} While it is quite easy to sit in an Institutional Review Board (IRB) meeting and design protections best suited to protect pediatric subjects from adverse harm of a proposed study, protections made to maximize the informed consent procedure are often blurred in the field. As detailed by review of multiple studies, this problem has many causes.\textsuperscript{166} Disparities in education and wealth between the researching nation and host nation, communication problems, and varying ethical beliefs with respect to appropriate informed consent procedures are just a few examples.\textsuperscript{167} Coupled with these factors, especially as it relates to impoverished nations such as Kenya, are the large discrepancies in which different cultures view health care providers and researchers.\textsuperscript{168} While America and other advanced nations often question many aspects of health care research, a much more accepting and paternalistic role of the health care provider exists in Kenya.

Morality of informed consent is context dependent. As applied from academia and institutional review board meetings, deep understanding of the subject’s risks in the research is of the utmost significance. As applied to the field researcher in a third world country where lack of education, extreme poverty, and a paternalistic culture exists, the preeminent informed consent

\begin{itemize}
  \item \textsuperscript{162} Id.
  \item \textsuperscript{163} Id.
  \item \textsuperscript{164} Id.
  \item \textsuperscript{165} Molyneux et al., supra note 121, at 445-45, 450.
  \item \textsuperscript{166} Id.
  \item \textsuperscript{167} Molyneux, Peshua, & Marsh, supra note 133, at 2547.
  \item \textsuperscript{168} Préziosi et al., supra note 157, at 370.
\end{itemize}
procedure is to tell as little ‘medical’ detail as possible so that the pediatric child can get what is often life-saving treatment via enrollment in the research study. Ethical principles surrounding the best manner for informed consent are indeed flexible, as multiple variables interplay to form the best health outcome, as well as the best perceived ethical and moral outcome.

VII. INTRODUCTION TO REGULATIONS FOR BIOMEDICAL RESEARCH IN INDIA

The first guidelines for biomedical research in India were created by The Indian Council of Medical Research. The Policy Statement on Ethical Considerations involved in Research on Human Subjects was created in 1980 and was revised in 2000 as the Ethical guidelines for Biomedical Research on Human Subjects. Varied versions of international biomedical research guidelines were released in 2002, and they included the revised Council for International Organizations of Medical Science (CIOMS) guidelines which focused on ethical norms relevant to research participants in developing nations. CIOMS guidelines were prepared in collaboration with the World Health Organization (WHO), and updated from the previous version which was primarily related to externally funded clinical trials taking place in low resource countries. At that time, India faced challenges with applying universal ethical principles to their multicultural society due to the varying standards of healthcare systems. To address this issue, India released a third version of the Ethical Guidelines for Biomedical Research on Human Participants, known as the Indian Council for Medical Research (ICMR) Code, consisting of two parts: (1) Statement of General Principles on Research using Human Participants in Biomedical Research and (2) Statement of Specific Principles on Research


170. ICMR Guidelines, supra note 169, at 1; see also COUNCIL FOR INT’L ORGS. MED. SCI. (CIOMS), INTERNATIONAL ETHICAL GUIDELINES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1993) [hereinafter CIOMS GUIDELINES].

171. CIOMS GUIDELINES, supra note 170.

172. Kumar, supra note 169, at 56.

173. ICMR GUIDELINES, supra note 169, at 1.
using Human Participants in specific areas of Biomedical Research.\textsuperscript{174} The new version of the ICMR Code was created with the hopes of covering new methods in biological sciences and biotechnology.\textsuperscript{175} While the latter part of the ICMR Code is not the subject of this paper, nor are there specific guidelines for pediatric research, it is helpful to know what areas of biomedical research and healthcare contain specific provisions to inform a comparative analysis. Part two of the ICMR Code provides specialized guidelines for research in the following areas: human genetics and genomics research; research in transplantation; research and evaluation of clinical drugs; vaccines; devices; and research on epidemiological studies.\textsuperscript{176} In the United States, no such specific research ethics provisions can be found codified in the federal register, except for provisions under the FDA.\textsuperscript{177}

Of particular interest is the flexibility of the statements, which according to the ICMR may be amended, substituted, varied, or added to "from time to time."\textsuperscript{178} The Indian research guidelines are meant to ensure that biomedical research on human subjects maintains a valid purpose, is conducted properly, and undergoes appropriate evaluation. This philosophical intent behind the ICMR Code is virtually synonymous to the role of the institutional review board, the C.F.R., and the Belmont Principles combined when viewing these from an U.S. perspective.

\section*{A. The Indian Biomedical Research Ethics Guidelines—The Philosophical and Practical Principles}

Similar to other guiding documents, the ICMR Code utilizes twelve principles as its foundation for the ethical treatment of human subjects in biomedical research.\textsuperscript{179} What follows is a brief explanation of each of the twelve ICMR Code principles, which in one way or another reflect the traditional research ethics principles used in both the United States and internationally.

\textsuperscript{174} Id. at 2.

\textsuperscript{175} Kumar, supra note 169, at 56.

\textsuperscript{176} ICMR GUIDELINES, supra note 169.

\textsuperscript{177} See generally 21 C.F.R. § 11 (1997).

\textsuperscript{178} ICMR GUIDELINES, supra note 169, at 2.

\textsuperscript{179} Id.
B. The Principle of Essentiality

The principle of essentiality is meant to ensure that the selected research subject is essential to conduct the research and lends to the mission of advancing knowledge for human benefit. In its present form, this principle extends further to include the caveat that the research also benefits the ecological and environmental wellbeing of the planet. Extending the principle of essentiality could have social, cultural, and religious ties to the Indian people through the Hindu religion.

C. Principles of Voluntariness, Informed Consent and Community Agreement

The next principle actually includes several principles: the principles of voluntariness, informed consent, and community agreement of the ICMR Code. These principles are consistent with documents such as the Belmont Report and the United States Federal Research Regulations which include informed consent as a foundational principle in research ethics. Like other guiding principles, this principle in the ICMR Code maintains that research participants must be fully aware of the risk and benefits of research and that the participant has the right to withdraw from the research regardless of any obligations already entered into—including legal contracts. The aspect of community in research participation differs in developing nations, including India. Where research entails treating any community or group of persons, the ICMR utilizes the term *mutatis mutandis* to explain that both the community and the individual person must give a mutual consent to participate in the research and understand changes of any particular relevance to all participants. In addition, this ICMR

180. *Id.* at 4.

181. *Id.* at 1.

182. *Id.*


185. ICMR GUIDELINES, supra note 169.

186. *Id.*
principle of informed consent and voluntariness includes the provision that when a fiduciary duty applies, the manner of consent may also include one person consenting for another.\textsuperscript{187}

D. The Principle of Non-Exploitation

The next principle elucidated in the ICMR is the principle of non-exploitation\textsuperscript{188} which, as a general rule, suggests that research participants are compensated for their involvement in the research, kept informed of all continuing risks and benefits of the research regardless of economic or health literacy status, and that research participant selection does not discriminate in any arbitrary manner.\textsuperscript{189} In the ICMR Code, this principle of non-exploitation goes further to include an insurance requirement that each research protocol will include a built-in mechanism for compensation for the human participants that covers all foreseeable and unforeseeable risks by providing remedial action including comprehensive aftercare, treatment pre- and post-research, and immediate rehabilitative measures for those affected.\textsuperscript{190}

E. The Principles of Privacy and Confidentiality

The next principle in the ICMR Code includes both universal principles of privacy and confidentiality. The principles of privacy and confidentiality\textsuperscript{191} reflect the general privacy requirements in all areas of medical practice in the United States. This ICMR Code principle requires adherence to privacy and non-disclosure practices while dealing with medical information when the identity and records of the human participants of the research are utilized.\textsuperscript{192} Furthermore, this principle in the ICMR Code requires efforts to eliminate potential stigmatization of research subjects for participating in the research.\textsuperscript{193}

\begin{itemize}
\item \textsuperscript{187} \textit{Id.}\n\item \textsuperscript{188} \textit{Id.}\n\item \textsuperscript{189} \textit{Id.}\n\item \textsuperscript{190} \textit{Id.}\n\item \textsuperscript{191} \textit{Id.}\n\item \textsuperscript{192} \textit{Id.}\n\item \textsuperscript{193} \textit{Id.}\n\end{itemize}
F. The Principles of Precaution and Risk Minimization

Minimizing risk to research participants is a universal goal,194 and the ICMR Code elaborates on this fact through its next principles: precaution and risk minimization. Like the United States, India has no means to truly quantify research risks for consenting adults; however U.S. federal guidelines require that a minimal risk standard is met for pediatric research participants.195 Approval for pediatric research studies requires that the protocol offers participants the 'prospect of direct' benefit and research that poses minimal risk or a minor increase over minimal risk.196

G. Principles of the Maximization of the Public Interest and Distributive Justice

In the ICMR Code, the principles of maximization of public interest and distributive justice reflect the idea that research should also benefit mankind as a whole.197 The community involvement principle instructs that there should be direct benefit to the community from which research participants are drawn, and India exemplifies this principle. In the United States, this trend is seen in Community Based Participatory Research (CBPR). CBPR is a model of research which values the role of community members and academicians as equitable partners. In CBPR, each partner makes unique contributions to the research process.198

Specific research methodology used in CBPR varies widely. Generally, however, CBPR projects value cooperative efforts between community members and researchers. Moreover, they strive to utilize the study results

194. CIOMS GUIDELINES, supra note 170.


197. ICMR GUIDELINES, supra note 169.

198. Introduction to Methods in Community-Based Participatory Research for Health, in METHODS IN COMMUNITY-BASED PARTICIPATORY RESEARCH FOR HEALTH, 7-8 (Barbara A. Israel et al., eds., 2005).
to the benefit of the participating communities.\textsuperscript{199} CBPR has gained popularity in areas of research that focus on health disparities, as well as with pediatric populations.\textsuperscript{200} While it is common for pediatric populations to be the subject of CBPR, it is often impractical to involve children and adolescents in the research process.\textsuperscript{201} While there are inherent challenges with involving children and adolescents in the details of the research process, community involvement is an important principle in biomedical research illustrated by both the United States and India.

\textbf{H. Principles of Institutional Agreements and Public Domain}

The ICMR Code specifies that research protocols contain specific institutional agreements and allow for dissemination of research results into the public domain.\textsuperscript{202} There is virtually no difference between these Indian principles and the general requirements for researchers and federal grant applications in the United States. The implications of adhering to these research principles allow for a transparent research process within multiple collaborators.

\textbf{I. Principles of Total Responsibility and Compliance}

The final two principles in the ICMR Code presume a total responsibility requirement for the researchers to maintain due diligence and to affirm a positive duty of compliance.\textsuperscript{203} Perhaps redundant in substance, yet distinct in language, these principles conclude with expressions relating to the binding nature of the Indian Biomedical Research Ethics Guidelines on


\textsuperscript{201} \textit{Id.}

\textsuperscript{202} ICMR \textit{GUIDELINES}, \textit{supra} note 169.

\textsuperscript{203} \textit{Id.}
researchers and institutions involved. In the United States, research compliance is enforced by regulatory agencies with many full-time institutional employees dedicated to the protection of human subjects in research.

J. Research Review Procedures in India—Institutional Ethics Committees

Similar to the U.S. IRBs, multidisciplinary Institutional Ethics Committees (IECs) evaluate risk in research protocols in India. Unfortunately, the ICMR Code is not legally binding. Thus, the urgently needed legal force to prevent exploitative research is unavailable. Additionally, IECs and IRBs are responsible for continuing review of protocols, which must accord with the Standard Operating Procedures of the World Health Organization (WHO). Without mandatory accreditation and registration of IECs, it is difficult to ensure that they are protecting human subjects. Recently, many IECs voluntarily joined accreditation through the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP), and the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRP). The increased utilization of CROs has caused critics to speak to the need for reform to the policies and procedures IECs follow in India.

204. ICMR GUIDELINES, supra note 169.


208. ICMR GUIDELINES, supra note 169.


VIII. CONCLUSION

Developing countries have taken steps to create comprehensive guidelines to direct human subjects research, but it is striking that there are very few guidelines specific to the inclusion of children and adolescents in research. While permissible in each country, their status as a “special” or a “vulnerable” population may be identified, but there is little concrete identification of what, if anything, that status guarantees.

The challenge of each of these developing countries is quite different. In China, guidelines for research, in general, are very similar to the U.S.; however, it is not clear that those guidelines are properly enforced. Moreover, key differences remain, such as China’s tradition of familial assent for medical decision-making. In Kenya, the treatment of children is so closely related to research that families do not always understand that they are participating in research and rarely question doctors’ advice. Finally, in India, subjects would be better protected if guidelines were enforced. However, due to the large population, India should focus on bioethics education, good clinical practice, and pharmacovigilance, which will lead to increased transparency in biomedical research. By better understanding the guidelines and cultural contexts of developing countries, research quality and international collaboration can improve.