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Protecting the Rights of Children as Human Subjects in Developing Countries: Revisiting Informed Consent

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Protecting the Rights of Children as Human Subjects in Developing Countries: Revisiting Informed Consent.

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Introduction

The globalization of biomedical research has led to the proliferation of clinical and drug trials in the developing countries. This is partly because of less stringent regulatory oversight, an eager pool of subjects¹ and lower research cost compared to sponsor countries.² A report issued by the Department of Health and Human Services ("HHS") Office of Inspector General ("OIG") in June 2010 confirmed that eighty percent of approved marketing applications for drugs and biologics contained data from trials conducted in foreign countries, and more than half of clinical trial subjects and sites were located overseas.³ The percentage of clinical trials conducted outside of the United States and registered by the Food and Drug Administration ("FDA"), has increased from five percent in 1997 to twenty-nine percent in 2007, with costs being a major driver for the outsourcing.⁴

¹ Gina Kolata, Companies Facing Ethical Issues As Drugs Are Tested Overseas, THE NEW YORK TIMES, March 5, 2004, at A1.

² 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, 18 (2003).

³ Daniel R. Levinson, *Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials*, OFFICE OF THE INSPECTOR GENERAL AT THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, June 2010 at 21, available at <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>

⁴ Steven W. Postal, et al., *After Guatemala and Nigeria: The Future of International Clinical Research Regulation*, 24 HEALTH LAW 1, 6 (October 2011).

Recently, there has been outcry regarding international research because of unethical protocols and in some cases human rights violations in populations that lack understanding of research, as certain populations may not consider the activity as research but as a way to receive unaffordable medical care. The concern for harm or injury in research involving vulnerable populations like children, pregnant women and fetuses, prisoners, persons with mental and behavioral disorders, illiterates, and terminally ill patients have increased because of some of these unethical protocols. Furthermore, industrialized countries benefit more from this research than developing countries where the studies are conducted due to financial gains acquired through product approval, marketing and high costs.⁵

Despite the existence of international protections for human subjects of research, some study investigators and sponsors have failed to provide subjects in developing countries with the same rights accorded research subjects in industrialized countries. Quite a number of clinical studies and trials conducted in developing countries have led to regulatory violations and have put vulnerable populations at risk.

This paper focuses on biomedical and pharmaceutical research involving unethical research in children in developing countries where the accepted international and United States' protections were lacking. Part I examines the international guidelines for the protection of vulnerable populations such as the Nuremberg Code, the Declaration of Helsinki, the International Covenant on Civil and Political Rights, the Council for International Organizations of Medical Sciences, and the Belmont Report as well as the United States' federal frameworks. Part II introduces the well-known Pfizer Trovan drug test in Nigeria in 1996 involving unethical research protocol, lack of informed consent and assent by the children involved. Part III

⁵ Daniel R. Levinson, *supra* note 3.

critically reviews the process of informed consent of parents and children with diverse socio-cultural background involved in the research vis-à-vis the international guidelines and United States' regulations for conducting biomedical research involving vulnerable populations. Part IV discusses the current changes to foreign research regulations and offers suggestions for improvement of informed consent process in developing countries.

I. Protection of Human Subjects in Research

A. International Protections/Ethical Frameworks

The international framework for protection of human subjects in research has its bedrock in the Nazi doctors' trial at Nuremberg, Germany. In 1947, the judges at the Nuremberg criminal trials formulated an international standard of human rights for patients involved in human experimentation, now known as the Nuremberg Code.⁶ The Nuremberg Code sets the international standards for all future ethical and legal questions pertaining to the conduct of human experimentation,⁷ and laid down informed consent as the foundation of all ethical research with human subjects. The Nuremberg Code (the "Code"), the Declaration of Helsinki (the "Declaration"), the International Covenant on Civil and Political Rights (ICCPR), the World Health Organization's CIOMS Guidelines ("CIOMS GUIDELINES"), and the Belmont Report are five major international guidelines for the protection of human subjects' right of informed consent in experimentation.

i. The Nuremberg Code

⁶ Carr, *supra* note 2 at 17, (citing Judges Harold Sebring, Walter Beals, & Johnson Crawford, *The Nuremberg Doctors' Trial: The Judgment*, in HEALTH AND HUMAN RIGHTS: A READER 292-300 (Jonathan M. Mann, et al. eds., 1999)).

⁷ Amy F. Wollensack, *Closing the Constant Garden: The Regulation and Responsibility of U.S. Pharmaceutical Companies Doing Research on Human Subjects in Developing Nations*, 6 WASH. U. GLOBAL STUD. L. REV. 747, 748 (2007) (citing Sharon LaFraniere, Mary Pat Flaherty & Joe Stevens, *The Body Hunters, Failure of Consent; The Dilemma; Submit or Suffer; 'Uninformed Consent' Is Rising Ethic of the Drug Test Boom*, WASH. POST, Dec. 19, 2001 at A1).

The trial of the Nazi doctors and scientists between 1946 and 1947 sets the international framework for the protection of human subjects in human experimentation.⁸ During the Second World War, the German doctors and scientists led by Dr. Karl Brandt, performed fatal experiments on inmates at the concentration camp without their consent.⁹ The human experimentation by the Nazi doctors demonstrated a complete disregard of the inherent value of human life and a total lack of compassion for the pains and sufferings of the test subjects.¹⁰

The unethical human experimentation performed by the Nazi doctors and scientists included the following: deliberate infection of subjects with malaria, typhus, yellow fever, smallpox, cholera, etc. (to test the efficacy of immunization and drugs); deliberate infliction of wounds and then infection with bacteria such as tetanus (to test the efficacy of sulfanilamide and other drugs); deliberate poisoning of subjects' food for poison experiments; and freezing experiments in which subjects were exposed for long hours to temperatures below the freezing points or forced to stay inside a tank of ice water.¹¹ The trial of the Nazi doctors and the Nazi atrocities revelations demonstrated to a shocked world that leaving research subject protection and welfare to the sole discretion of an investigator raises the potential for abuses.¹²

⁸ Carr, *supra* note 2 at 20.

⁹ Remigius N. Nwabueze, *Ethical Review of Research Involving Human Subjects In Nigeria: Legal and Policy Issues*, 14 IND. INT'L & COMP. L. REV. 87, 94 (2003-2004).

¹⁰ Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT'L L. 513, 521(2002), (citing Telford Taylor, *Opening Statement of the Prosecution, December 9, 1946, reprinted in* GEORGE J. ANNAS & MICHAEL A. GRODIN, *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN EXPERIMENTATION* 231 (1992)), at 67 ("The defendants in this case are charged with murders, tortures, and other atrocities committed in the name of medical science To their murders, these wretched people were not individuals at all. They came in wholesale lots and were treated worse than animals.").

¹¹ Meier, *supra* note 10 at 521, (citing UNITED STATES V. KARL BRANDT, 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 (1948), REPRINTED IN JAYS KATZ, *EXPERIMENTATION WITH HUMAN BEINGS: THE AUTHORITY TO THE INVESTIGATOR, SUBJECT, PROFESSIONS, AND STATE IN THE HUMAN EXPERIMENTATION PROCESS* 293 (1972)).

¹² Kevin M King, *A Proposal For The Effective International Regulation of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT'L L. 163, 165 (1998). See also, Nwabueze, *supra* note 9, (citing M. GRODIN, *Historical Origin of Nuremberg Code, in* THE NAZI DOCTORS AND NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 121-44 (G.J. ANNAS & M. GRODIN EDS., 1992); Matthew Lippman, *The Nazi Doctors Trial and the International Prohibition on Medical Involvement in Torture*, 15 LOY. L.A. INT'L COMP. L.J. 410 (1993)).

In the aftermath of the Second World War, twenty-three Nazi Doctors and scientists were accused of war crimes and crimes against humanity and were prosecuted before the Military Tribunal at Nuremberg, Germany.¹³ The Nuremberg Code is based on natural law and it protects the rights of a subject over the researcher's right to his or her scientific endeavor.¹⁴ The Nuremberg Code provides, *inter alia*: (1) the voluntary and informed consent of the subjects in human experimentation; (2) the experiment must yield fruitful results for the good of society that would not have been procurable by any other methods or means; (3) the experiment should be conducted as to avoid all unnecessary physical and mental suffering and injury to subjects; (4) the degree of risk should be minimal to the subject; (5) the experiment must be conducted only by scientifically qualified persons; and (6) in the course of the experiment the subject should be at liberty to terminate the experiment where continuation seems impossible to him and the researcher must terminate the experiment if he believes that it may cause harm and injury to the subject.¹⁵ The research subjects cannot voluntarily waive any of the requirements.¹⁶ The principles of the Nuremberg Code set the ethical framework for the United States federal regulations and the international guidelines for the conduct of biomedical research.¹⁷

Even though the Nuremberg Code has been regarded as the first source of international law laying the foundation for all human subject research, it lacked legal force on the individual

¹³Meier, *supra* note 10 at 522-523, (citing UNITED STATES V. KARL BRANDT, 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 (1948), REPRINTED IN JAYS KATZ, EXPERIMENTATION WITH HUMAN BEINGS: THE AUTHORITY TO THE INVESTIGATOR, SUBJECT, PROFESSIONS, AND STATE IN THE HUMAN EXPERIMENTATION PROCESS 296 (1972)).

¹⁴ Joanne Roman, *U.S. Medical Research In The Developing World: Ignoring Nuremberg*, 11 CORNELL J.L. & PUB. POL'Y 441, 448 (2002).

¹⁵ The Nuremberg Code, *reprinted from* Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949, available at <http://www.hhs.gov/ohrp/archive/nurcode.html> (Last visited Dec. 8, 2013).

¹⁶ Roman, *supra* note 14 at 449.

¹⁷ Wollensack, *supra* note 7 at 749, (citing Michael A. Grodin, *Historical Origins of The Nuremberg Code*, in THE NAZI DOCTORS AND NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 121, 139 (GEORGE J. ANNAS & MICHAEL A. GRODIN, EDS., 1992)).

states or countries,¹⁸ and has had little impact on the entire world as its existence has not prevented subsequent research scandals.¹⁹ Physicians and scientists have continued throughout the world to use human subjects in medical research without proper consent or adequate disclosure of the research to the subjects.²⁰

ii. The Declaration of Helsinki

The Nuremberg Code is criticized due to its lack of legal force and the fact that it relies entirely on the researcher to follow the principles set by the code. These led to the promulgation of a set of ethical standards by the medical researchers' community. The Declaration of Helsinki²¹ ("the Declaration") was issued in 1964 by the World Medical Association (WMA). It "was the first international regulation written by physicians for physicians,"²² as a direct response to the problems perceived in the Nuremberg Code. The goal of the Declaration was to establish a more relaxed medical ethics model that permitted paternalism, expressing a more "benign modern attitude toward biomedical research."²³

The Declaration provides guidance for physicians conducting human subjects' research,²⁴ unlike the Nuremberg Code that merely emphasizes voluntary consent as "absolutely essential,"²⁵ the Declaration specifically requires that the subject's "freely given informed consent" should be obtained after the subject fully understands the details of the research,

¹⁸ Meier, *supra* note 10 at 524.

¹⁹ *Id.*

²⁰ *Id.*, (citing HENRY K. BEECHER, RESEARCH AND THE INDIVIDUAL: HUMAN STUDIES (1970); M.H. PAPPWORTH, HUMAN GUINEA PIGS: EXPERIMENTATION ON MAN (1968)).

²¹ The Declaration of Helsinki, WMA 64th General Assembly, Fortaleza, Brazil, October 2013 (the current version), available at <http://www.wma.net/en/30publications/10policies/b3/> (Last visited Dec. 8, 2013).

²² Meier, *supra* note 10 at 525.

²³ Roman, *supra* note 14 at 452.

²⁴ 1964 Declaration of Helsinki provides that "in any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time," § I.9.

²⁵ Nuremberg Code, Principle I (1947), reprinted in 313 Brit. Med. J. 1448, 1448 (1996).

“preferably in writing, formally documented and witnessed.”²⁶ The 1964 Declaration of Helsinki has undergone multiple revisions and there have been two notes of clarification added.²⁷ The sections on informed consent were strengthened with regards to vulnerable subjects, requiring the physician to exercise special caution when the subjects cannot give or refuse consent for themselves²⁸ and those who may be vulnerable to coercion or duress.²⁹

In addition, the Declaration allows consent by proxy from the legal representative of the subject in cases of legal or mental incompetence or physical incapacity.³⁰ In cases where proxy consent cannot be obtained, such as unconscious homeless patients, research should only be done if the condition preventing legal competence is a necessary characteristic of the research population.³¹

To protect the consent process, the Declaration provides that research protocol must be submitted for review to an independent research ethics committee.³² The committee must be independent of the researcher, the sponsor and any other undue influence and must take into consideration the applicable international norms, laws and regulations of the country wherein the

²⁶ The Declaration, *supra* note 21, Principle 26.

²⁷ The Declaration, *supra* note 21. The Declaration of Helsinki was amended in 1975, 1983, 1989, 1996, 2000, 2008 and 2013 with notes of clarification added in 2002 and 2004.

²⁸ The Declaration recognizes the need for special protection for “vulnerable” individuals participating in research, defining “vulnerable” as those who cannot give consent themselves, such as children, *supra* at note 23, principles 19 and 20. In some countries, certain classes of persons are not legally given the right to consent for themselves: such as children, women, those suffering from mental disabilities, and other potentially vulnerable groups. *See also* David M. Carr, *supra* note 2 at 23, (citing Ruth Macklin, *University of the Nuremberg Code, in THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* 240, 251 (GEORGE J. ANNAS & MICHAEL A. GRODIN EDS., 1992)).

²⁹ The Declaration, *supra* note 21, Principle 27.

³⁰ *Id.*, Principle 30.

³¹ *Id.*, Principles 28 and 30. The Declaration provides that “in such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.”

³² The Declaration, *supra* note 21, Principle 23.

research is to be performed and standards must not reduce or eliminate any of the protections prescribed in the Declaration.³³

The Declaration of Helsinki, states that “medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects ... and must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.”³⁴

The Declaration of Helsinki, like the Nuremberg Code lacked legal force despite the fact that it was the first international regulation written by physicians for physicians. It is merely a guidance document for conducting human subjects’ research.

iii. The Council for International Organizations of Medical Sciences (CIOMS)

Guidelines

The World Health Organization (WHO) and the Council for International Organizations of Medical Sciences³⁵ (CIOMS) enacted the International Guidelines for Biomedical Research

³³ The Declaration, *supra* note 21, Principle 10. Some other relevant provisions of the Declaration include that: (1) only trained and qualified persons should perform research; (2) research should be preceded by assessment of predictable risks and benefits; (3) research should only be conducted if its importance outweighs potential burdens to subjects; (4) research must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research; (5) participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees; (6) authors, editors, publishers as well as researchers all have ethical obligations with regard to the publication of the results of research; (7) the refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the medical care rendered; and (8) appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

³⁴ The Declaration, *supra* note 21, Principles 16 and 17.

³⁵ CIOMS is an international, non-governmental organization established by the WHO and United Nations Educational, Scientific and Cultural Organization (“UNESCO”) in 1949. The main objectives of CIOMS are to promote international biomedical activities, serve the scientific interests of the international biomedical community, and to maintain collaborative relations with the WHO and the United Nations and its specialized agencies. See International Ethical Guidelines for Biomedical Research Involving Human Subjects, *available at* http://www.cioms.ch/publications/layout_guide2002.pdf.

Involving Human Subjects (“the CIOMS Guidelines”).³⁶ The CIOMS Guidelines requires that each individual give voluntary informed consent and in case of incompetent individuals, the permission of the legal representative must be obtained before participating in experimental research.³⁷

The CIOMS Guidelines requires that a physician or scientist when obtaining informed consent for research, informs the potential patient or subject, of the nature, purpose, methods, risks and benefits, the expected duration of the research, alternative treatments available, expected benefit to the community, and that the subject is free to refuse to participate or withdraw from the research at any time without fear of losing medical care being offered.³⁸ CIOMS Guidelines also expands protections for vulnerable populations³⁹ and categorizes children as a “vulnerable population” who require special protection.⁴⁰ With research involving children, the CIOMS Guidelines provides that investigator must ensure that: the research might not equally well be carried out with adults; the purpose is to obtain knowledge relevant to health needs of children; a parent or legal guardian of each child has given consent; assent of each child has been obtained to the extent of each child’s capabilities; and a child’s refusal to participate or continue in the research is respected.⁴¹

³⁶ International Ethical Guidelines for Biomedical Research Involving Human Subjects reprinted in *Ethics and Research on Human Subjects: International Guidelines* 231 (Z. Bankowski & R.J. Levine eds., 1993), available at http://www.cioms.ch/publications/layout_guide2002.pdf. (CIOMS Guidelines).

³⁷ CIOMS Guidelines, *supra* note 36, Guideline 4.

³⁸ Carr, *supra* note 2, at 25-26. See also CIOMS Guidelines, *supra* note 36, Guideline 5.

³⁹ CIOMS Guidelines, *supra* note 36, Guideline 13, defines “vulnerable populations” as “those who are relatively incapable of protecting their own interests,” due to insufficient power, education, intelligence, resources, strength, or other needed attributes to protect their own interest.

⁴⁰ *Id.*, Commentary on Guideline 13. Other vulnerable populations include: (1) persons with mental or behavioral disorders; (2) prospective subjects who are junior or subordinate members of a hierarchical group; (3) poor people; (4) racial minority groups, and (5) politically powerless persons.

⁴¹ *Id.*, Guideline 14.

The CIOMS Guidelines, like the Declaration of Helsinki, requires Independent Ethical Review Committee to review research protocols prior to study commencement.⁴² In addition, the CIOMS Guidelines also provides for non-waiver of the right of injured subjects to treatment and compensation,⁴³ and allows sanctions to be imposed by the hosting state when researchers violate local or international standards of ethical conduct in experimental research.⁴⁴

iv. International Covenant on Civil and Political Rights

The ICCPR is part of the International Bill of Human Rights, along with the International Covenant on Economic, Social and Cultural Rights (ICESCR) and the Universal Declaration of Human Rights (UDHR).⁴⁵ In response to Nazi human experimentation during the World War II, United Nations incorporated the informed consent doctrine in the context of human experimentation in Article 7 of the International Covenant on Civil and Political Rights (ICCPR).⁴⁶ The ICCPR is the “only legally binding international treaty concerning human experimentation”⁴⁷ and states or countries ratifying the treaty must comply with its terms,⁴⁸ and as such it has cemented the international status of the Nuremberg Code on the consent

⁴² *Id.* Guideline 2. See also King, *supra* note 12, at 183. Unlike the Declaration of Helsinki (prior to 1989), the CIOMS Guidelines requires an independent ethic review committee to approve all experiments involving human research subjects.

⁴³ CIOMS Guidelines, *supra* note 36, Guideline 19. The CIOMS Guidelines distinguishes between those entitled to free medical treatment and compensation due to accidental injury during research (non-therapeutic procedures) and entitlement of dependants to material compensation for death or disability occurring as a result of direct participation in the study.

⁴⁴ *Id.*

⁴⁵ "[Fact Sheet No.2 \(Rev.1\), The International Bill of Human Rights](#)". United Nations Office of the High Commissioner for Human Rights, June 1996. Archived from the original on 13 March 2008. (Last visited Nov. 23, 2013).

⁴⁶ International Covenant on Civil and Political Rights, December 19, 1966 (entered into force March 23, 1976) [hereinafter ICCPR], available at <http://www.ohchr.org/en/professionalinterest/pages/ccpr.aspx> (Last visited Dec. 8, 2013).

⁴⁷ Kristen Farrell, *Human Experimentation In Developing Countries: Improving International Practices By Identifying Vulnerable Populations and Allocating Fair Benefits*, 9 J. HEALTH CARE L. & POL'Y 136, 143 (2006), (citing Finnuala Kelleher, Note, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J.L. & SOC. PROBS. 73 (2004)).

⁴⁸ ICCPR, *supra* note 46, Article 50.

requirement.⁴⁹ Article 7 states 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.”⁵⁰ The United Nations’ principle of informed consent, “equates un-consented medical experimentation to torture and cruel, inhuman, and degrading treatment.”⁵¹ The prohibition stated in Article 7, guarantees individuals the right to be free from any nonconsensual medical experimentation by any entity whether state or private actors.

v. The Belmont Report

The National Research Act of 1974 created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges of National Commission “was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.”⁵² The Belmont Report was issued on September 30, 1978 and was originally published on April 18, 1979 and it established three basic ethical principles: respect for persons,⁵³ beneficence⁵⁴ and justice.⁵⁵ There are three applications for these ethical principles:

⁴⁹ Joanne Roman, *supra* note 14 at 449.

⁵⁰ ICCPR, *supra* note 46.

⁵¹ Wollensack *supra* note 7, at 751.

⁵² National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979) [hereinafter The Belmont Report], available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html> (Last visited Dec. 8, 2013).

⁵³ *Id.* The principle of respect for persons incorporates at least two ethical convictions; first that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. This principle requires that a person be given the opportunity to decide what should or should not happen to him.

⁵⁴ *Id.* The principle of beneficence comprises “two general rules of (1) do not harm and (2) maximize possible benefits and minimize possible harms.”

⁵⁵ *Id.* The principle of justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper and also to give each person what is due to him or her. According to the Belmont Report, “an injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly.”

individual voluntary informed consent;⁵⁶ assessment of risks and benefits;⁵⁷ and selection of subjects.⁵⁸

The objective of the Belmont Report is “to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.”⁵⁹ However, “unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department’s policy.”⁶⁰ The Belmont Report now serves as a historical document and provides the moral framework for understanding regulations in the United States on human experimentation.

Even though the Belmont Report has been instrumental to setting the ethical framework on human subjects’ protection in the United States, it has been criticized for failing to provide guidance to Institutional Review Boards (IRBs) and researchers in interpreting and applying its provisions to individual research studies.⁶¹ The IRBs and researchers are believed to have focused largely on the legal requirements imposed by the Federal regulations while overlooking the Belmont Report in reviewing research protocols and conducting research.⁶²

⁵⁶ *Id.* The requirement of individual voluntary informed consent derived from respect for persons entails the extent and nature of information provided should be such that a reasonable person could adequately decide whether or not to participate in the research and such information should be conveyed in a manner and context that the subject could understand.

⁵⁷ *Id.* The requirement of assessment of risk and benefit is derived from the principle of beneficence. This entails the nature and scope of the risks and benefits and the systematic assessment of risks and benefit. It is a method of determining whether the risks that will be presented to subjects are justified.

⁵⁸ *Id.* The principle of justice finds its application in the requirement that the burdens and benefits of research be equitably distributed. There are two levels relevant to the selection of subjects: social and individual. It is an obligation to treat people with fairness.

⁵⁹ The Belmont Report, *supra* note 52.

⁶⁰ *Id.*

⁶¹ Alice K. Page, *Ethical Issues in International Biomedical Research: An Overview*, 37 J. HEALTH L. 629, 638, (2004).

⁶² *Id.*

The Nuremberg Code, the Declaration of Helsinki, CIOMS Guidelines, the ICCPR and the Belmont Report all set the ethical frameworks for protecting the rights of human subjects in biomedical research. As earlier mentioned, the Nuremberg Code sets the ethical framework for the United States federal regulations while the Belmont Report sets the moral framework to comprehend regulations on human experimentation in the United States. All these documents emphasize the importance of informed consent, the provision of information on risks and benefits of the research and the right of subjects to refuse to participate or withdraw at any time from the research without fear of any repercussion.

A. US Regulations on Foreign Research

The United States has promulgated regulations addressing research involving human subjects and the protection for human research subjects is heavily influenced by the Belmont Report. The Federal Regulations, Title 45 of the Code of Federal Regulations, Part 46 (hereinafter “the Common Rule”) issued by the Department of Health and Human Services (DHHS)⁶³ provide ethical guidelines for research involving human research subjects. When research involves pharmaceutical research, the federal government imposes regulation through the Food and Drug Administration (FDA) and these regulations are substantially similar to the DHHS regulations. All clinical investigations that support applications for research or marketing permits for products regulated by the FDA are subject to the FDA regulations.⁶⁴ Human subjects’ research involving products regulated by the FDA must comply with both the

⁶³ The United States Policy for the Protection of Human Subjects published 1991, *available at* <http://www.hhs.gov/ohrp/humansubjects/commonrule/> (Last visited Dec. 8, 2013).

⁶⁴ FDA’s Protection of Human Subjects: Title 21 of the Code of Federal Regulations, Part 50 (2013), *available at* <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.1> (Last visited Dec. 8, 2013).

Common Rule if it receives federal funding and FDA regulations governing human subject protections.⁶⁵

i. Federal Regulations – The Common Rule

The DHHS regulates human subjects' research in federally funded research⁶⁶ through its Office for Human Research Protection (OHRP). The OHRP is charged with the basic responsibility for developing and implementing the policies, procedures and regulations to protect human subjects within the United States.⁶⁷ The OHRP required each institution engaged in research to establish IRBs.⁶⁸ The Common Rule requirements for IRB includes: membership,⁶⁹ review of research,⁷⁰ criteria for approval of research,⁷¹ record-keeping,⁷² and the documentation of informed consent.⁷³

The Common Rule requires that researchers satisfy informed consent requirements, including providing an explanation to human subjects; the purposes of the research, the expected duration, a description of the procedure, and identification of any procedures which are experimental.⁷⁴ Also, research subjects must be informed of any reasonably foreseeable risks or discomforts;⁷⁵ provided with a description of any benefits expected from the research;⁷⁶ as well as appropriate alternative procedures or treatments.⁷⁷ When research involves more than minimal risk, an explanation as to compensation or medical treatment if injury occurs must be

⁶⁵ Title 45 C.F.R. § 46.103 (2009).

⁶⁶ Title 45 C.F.R. § 46.101 (2009).

⁶⁷ Press Release, U.S. Department of Health and Human Services, New Office for Human Research Protections Created, Dr. Greg Koski Named Director (June 6, 2000), *available at* <http://archive.hhs.gov/news/press/2000pres/20000606.html>.

⁶⁸ Title 45 C.F.R. § 46.103(b) (2) (2009).

⁶⁹ Title 45 C.F.R. § 46.107 (2009).

⁷⁰ Title 45 C.F.R. § 46.109 (2009).

⁷¹ Title 45 C.F.R. § 46.111 (2009).

⁷² Title 45 C.F.R. § 46.115 (2009).

⁷³ Title 45 C.F.R. § 46.117 (2009).

⁷⁴ Title 45 C.F.R. § 46.116(a) (1) (2009).

⁷⁵ Title 45 C.F.R. § 46.116 (a) (2) (2009).

⁷⁶ Title 45 C.F.R. § 46.116(a) (3) (2009).

⁷⁷ Title 45 C.F.R. § 46.116 (a) (4) (2009).

provided to the research subject.⁷⁸ In addition, a statement that participation is voluntary and that refusal to participate or withdraw from the study will not result in any repercussion must be provided to research subjects.⁷⁹

The Common Rule provides additional protection for children involved as subjects for research⁸⁰ conducted or supported by the DHHS.⁸¹ The Common Rule provides that the DHHS will only conduct or fund research under the following conditions: (1) research that the IRB finds to present no greater than minimal risk to children and that adequate provisions are made for obtaining the assent of the children and the permission of their parents or guardians;⁸² (2) research involving greater than minimal risk but presents the prospect of direct benefit for the individual subject;⁸³ (3) research involving greater than minimal risk with no prospect of direct benefit but likely to yield generalizable knowledge about subject's disorder or condition;⁸⁴ and (4) research not otherwise approvable but presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children.⁸⁵ With regards to informed consent requirement, the Common Rule requires parents' or guardians' permission and assent by children.⁸⁶

The Common Rule, like the international documents setting the ethical frameworks for human subjects' research, stresses the essence of informed consent, the provision of information

⁷⁸ Title 45 C.F.R. § 46.116 (a) (6) (2009).

⁷⁹ Title 45 C.F.R. § 46.116 (a) (8) (2009). *See generally* Title 45 C.F.R. § 46.116 (2009) General requirements for informed consent. *See also* Title 21 C.F.R. § 50.20 (2013) for FDA's similar provisions.

⁸⁰ Title 45 C.F.R. Part 46, Subpart D. *See also* Title 21 C.F.R. Part 50, Subpart D on similar FDA protections for children in human research.

⁸¹ Title 45 C.F.R. § 46.401 (2009).

⁸² Title 45 C.F.R. § 46.404 (2009). *See also* FDA's provisions Title 21 C.F.R. § 50.51 (2013).

⁸³ Title 45 C.F.R. § 46.405 (2009). *See also* FDA's provisions Title 21 C.F.R. § 50.52 (2013).

⁸⁴ Title 45 C.F.R. § 46.406 (2009). *See also* FDA's provisions Title 21 C.F.R. § 50.53 (2013).

⁸⁵ Title 45 C.F.R. § 46.407 (2009). *See also* FDA's provisions Title 21 C.F.R. § 50.54 (2013).

⁸⁶ Title 45 C.F.R. § 46.408 (2009). *See also* FDA's provisions Title 21 C.F.R. §§ 50.52 (c) and 50.55 (2013).

on risks and benefits, and the right to withdraw or refuse to participate in research without fear of losing the medical care being provided.

ii. The Food and Drug Administration (FDA) Regulations – 21 C.F.R. Part 50

Title 21 of the Code of Federal Regulations, Part 50, “Protection of Human Subjects,” is the FDA’s regulations governing research involving human subjects. The FDA requires adherence to the informed consent requirements for research aimed at marketing a drug in the United States. Section 50.20, like the Common Rule, provides that: “... no investigator may involve a human being as a subject in research ... unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.”⁸⁷ In the same vein, 21 C.F.R. section 50.27 provides that “informed consent shall be documented by the use of a written consent form approved by the IRB, signed and dated by the subject or the subject’s legally authorized representative at the time of consent. A copy shall be given to the person signing the form.”⁸⁸

The FDA like the Common Rule emphasizes the significance of informed consent, the role of the subject’s legal representative, and most especially minimization of the possibility of coercion of subjects participating in research.

II. Clinical Trials/Studies in Developing Countries involving Children

⁸⁷ Title 21 C.F.R. § 50.20 (2013).

⁸⁸ Title 21 C.F.R. § 50.27 (2013).

A. Pfizer’s Trovafloxacin Mesylate (Trovan) Test in Nigeria, 1996 (“the Nigerian Study”)

The World Health Organization (WHO) on February 19, 1996 reported the outbreak of meningitis in nine States in the northern part of Nigeria, with Kano and Bauchi states having the most cases.⁸⁹ The 1996 meningitis epidemic was the worst ever with more than 3,000 deaths and several thousand victims suffering from the disease.⁹⁰ Pfizer, an international pharmaceutical company, conducted a clinical trial of its new antibiotic, Trovan during this epidemic of meningococcal meningitis in children in Kano, Nigeria in April 1996.⁹¹ At about the same time, Pfizer was in the process of conducting clinical trials,⁹² but because animal studies indicated that Trovan use may be associated with complications such as bone deformities, joint diseases and liver injury,⁹³ clinical studies involving human subjects could not be conducted in America. A physician, Scott Hopkins, working with Pfizer learned about the Nigerian meningitis outbreak⁹⁴ and advised Pfizer of the opportunity to test Trovan in affected children.⁹⁵

The Nigerian study team was comprised of three of Pfizer’s American physicians and four Nigerian doctors with Dr. Abdulhamid Isa Dutse (Dr. Dutse) as the lead investigator.⁹⁶ The Nigerian study was conducted at Kano’s Infectious Disease Hospital (“IDH”).⁹⁷ Pfizer’s new antibiotic, Trovafloxacin Mesylate (Trovan), now pending approval from FDA for use on children, was administered orally to one hundred sick children while another one hundred sick

⁸⁹ World Health Organization, *Global Alert and Response (GAR), Cerebrospinal Meningitis in Nigeria, Disease Outbreaks Reported* (Feb. 19, 1996), available at http://www.who.int/csr/don/1996_02_19c/en/ (Last visited Oct. 17, 2013).

⁹⁰ Carr, *supra* note 2, at 28.

⁹¹ Ruth Macklin, *Bioethics, Vulnerability, and Protection*, *Bioethics* ISSN 1467-8519 (online), Vol. 17, 475 (2003). *See also* Carr, *supra* note 2 at 29.

⁹² Wollensack, *supra* note 7 at 756.

⁹³ Wollensack, *supra* note 7 at 756. *See also* Abdullahi v. Pfizer, Inc., 2002 WL 31082956, *1 (S.D.N.Y. 2002) (*Abdullahi I*)

⁹⁴ Wollensack, *supra* note 7 at 756.

⁹⁵ *Id.*

⁹⁶ *Abdullahi I*, *supra* note 93 at *1.

⁹⁷ *Id.*

children received a cephalosporin antibiotic (ceftriaxone) at a reduced dose, an FDA-approved antibiotic - the standard anti-meningitis treatment but at a reduced dose.⁹⁸ At the end of the two week clinical trial, Pfizer's research team left Kano and never returned for follow-up evaluations.⁹⁹ Following the clinical trial, a total of eleven children died: five children who were administered Trovan and six who were administered ceftriaxone.¹⁰⁰ Several children were left blind, deaf, paralyzed, or brain-damaged.¹⁰¹

After the conclusion of the Nigerian Trovan Study, Pfizer applied to the FDA for approval of the medication for pediatric use in the United States. Pfizer later withdrew its application to use Trovan for epidemic meningitis when the FDA discovered some discrepancies in the data while auditing the Nigerian study documents.¹⁰² Specifically, the FDA informed Pfizer of its plan to deny Pfizer's application to use the Trovan to treat epidemic meningitis and also expressed concern about Pfizer's failure to conduct follow-up examinations.¹⁰³ However, Trovafloxacin was approved for marketing in the United States in December, 1997 for fourteen other types of serious infections and it became available on the market in February, 1998.¹⁰⁴ In July 1998, the FDA received over 100 post marketing reports linking Trovan use to serious liver injury including four cases that required liver transplantation and the use of the drug was suspended.¹⁰⁵

⁹⁸ *Abdullahi I, supra note 93 at *2.*

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² Wollensack, *supra note 7, at 757. See also Abdullahi I, supra note 93 at *2.*

¹⁰³ *Abdullahi I, supra note 93 at *2.*

¹⁰⁴ Murray M. Lumpkin, *Food and Drug Administration 09 June 1999 Trovan (Trovafloxacin/Alatrofloxacin Mesylate) INTERIM RECOMMENDATIONS*, available at <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/publichealthadvisories/ucm053103>

¹⁰⁵ *Id. See also Wollensack, supra note 7 at 757-758.*

The Nigerian study was tainted with the discovery of falsified ethics committee approval letter produced by Dr. Dutse.¹⁰⁶ The letter was said to have been backdated by Nigerian officials working at IDH well after the completion of the study and at a time when there was no ethic committee at the IDH¹⁰⁷ in response to a 1997 FDA audit.¹⁰⁸

B. The Pfizer's Trovan Litigation

In August 2001, the survivors of the Nigerian Study and their representatives sued Pfizer in *Abdullahi v. Pfizer, Inc.*, 2nd Cir. (N.Y.), 2002 WL 31082956 under the Alien Tort Statute (ATS) and alleged that the experiment violated law of nations as advised by the Nuremberg Code, the Declaration of Helsinki, the International Covenant on Civil and Political Rights (the “ICCPR”) and customary international law.¹⁰⁹

The plaintiffs alleged that Pfizer never informed them that they were part of a clinical trial, that Pfizer failed to obtain informed consent from the children, their parents or their guardians and that the experiment “exposed them to cruel, inhuman and degrading treatment.”¹¹⁰ The plaintiff also alleged that Pfizer never gave them the option of choosing alternative treatment, because they were never informed that Doctors Without Borders was administering the effective treatment free of charge in another section of the building.¹¹¹ Pfizer was also accused of orally administering Trovan to sick children despite that oral absorption was difficult for sick children, failure to conduct testing prior to Trovan administration to determine that children in the test had meningitis; and failure to either exclude children with liver or joint problems from the experiment or to test for such problems.¹¹² Plaintiff also accused Pfizer for

¹⁰⁶ *Abdullahi I, supra* note 93 at *2.

¹⁰⁷ *Abudullahi I, supra* note 93 at *1.

¹⁰⁸ *Abdullahi I, supra* note 93 at *2.

¹⁰⁹ *Abudullahi I, supra* note 93 at *1.

¹¹⁰ Wollensack, *supra* note 7 at 758.

¹¹¹ *Abdullahi I, supra* note 93 at *2.

¹¹² *Id.*

not following its research protocol which called for switching children not responding well to Trovan to Ceftriaxone.¹¹³ Finally, the plaintiffs alleged that Pfizer also failed to conduct regular blood tests of children or switch those who suffered from Trovan-related side effects to Ceftriaxone.¹¹⁴

In September 2002, the district court dismissed plaintiffs' claims for *forum non conveniens*.¹¹⁵ The district court concluded that Nigeria provided an adequate alternative forum, that Pfizer consented to litigation in Nigeria and that Nigeria has a strong interest in the litigation.¹¹⁶ Representative Tom Lantos of California, the senior Democrat on the House International Relations Committee in May 2006, described the findings of a report compiled about the case by the Nigerian government as "absolutely appalling," and called for Pfizer to open its records.¹¹⁷

The plaintiffs in *Abdullahi v. Pfizer* appealed the district court's dismissal of their suit on the basis of *forum non conveniens* to the United States Court of Appeals for the Second Circuit.¹¹⁸ In January 2009, the Court of Appeals for the Second Circuit ruled that the Nigerian victims and their families were entitled to bring suit against Pfizer in the United States under the Alien Tort Statute, stating that the "prohibition on nonconsensual medical experimentation on human beings constituted a universally accepted norm of customary international law, and consequently an alleged violation" that fell within the jurisdiction of Alien Tort Statute.¹¹⁹

Following the Second Circuit's reversal of the district court's decision, in February 2011, Pfizer settled all remaining cases filed in Nigeria by the Nigerian government and in New York

¹¹³ *Id.*

¹¹⁴ *Id.*

¹¹⁵ *Abdullahi I*, *supra* note 93 at *12.

¹¹⁶ *Id.* See also Wollensack, *supra* note 7 at 759.

¹¹⁷ Joe Stephens, *Panel Faults Pfizer in '96 Clinical Trial in Nigeria*, THE WASHINGTON POST, May 7, (2006), available at <http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html>.

¹¹⁸ *Abdullahi v. Pfizer, Inc.*, 562 F.3d 163 (2nd. Cir. 2009).

¹¹⁹ *Id.*

by parents and guardians¹²⁰ for \$75 million; the settlement was subject to a confidentiality clause.¹²¹

Another example of human subject research involving children in developing countries was the proposed “Testing a New Surfactant in Bolivia.”¹²² In 2000, Discovery Laboratories of Doylestown, Pennsylvania, proposed a phase 3 study to test the efficacy of a new drug called Surfaxin for treating idiopathic respiratory distress syndrome (“RDS”) in premature newborn infants in a placebo controlled study in Bolivia and three other Latin American countries.¹²³ The study population would consist of 650 premature infants with RDS in a double-blinded, randomized, two–arm placebo-controlled trial,¹²⁴ with a control group of 325 premature infants to be treated with placebo.¹²⁵

Surfactant was unavailable for treatment of RDS at the proposed hospitals for the study and the sponsor proposed to provide training, support, the necessary equipment and antibiotics for all study subjects.¹²⁶ For the proposed study, the “parents of the infants with RDS symptoms would be asked to give consent for their infants to participate in the study.”¹²⁷ Once consent has been obtained, the infants would be intubated with an endotracheal tube by a health care

¹²⁰ Steven W. Postal, et al., *A Remedy in Sight: International Clinical Research Regulation in the Wake of Guatemala and Nigeria*, 6 PITT. J. ENVTL PUB. HEALTH L. 1, 21 (2011).

¹²¹ *Id.* The Nigerian Kano State government filed both civil and criminal charges against Pfizer in 2007. The Nigerian federal government also sued Pfizer and individual employees for billions of dollars in damages. See also Joe Stephens, *Pfizer to Pay \$75 Million to Settle Trovan-Testing Suit*, THE WASHINGTON POST, July 31, (2009), available at http://articles.washingtonpost.com/2009-07-31/news/36811829_1_trovan-pfizer-chief-executive-william-c-steere. There have been a lot of scholarly written articles on the *Abdullahi* Litigation, for more detailed account and analysis, see Amy F. Wollensack, *Closing the Constant Garden: The Regulation and Responsibility of U.S. Pharmaceutical Companies Doing Research on Human Subjects in Developing Nations*, 6 WASH. U. GLOBAL STUD. L. REV. 747 (2007).

¹²² The Proposed Bolivia Study.

¹²³ Fred Charatan, *Surfactant trial in Latin American Infants criticized*, BMJ 322:575.3, 2001, (Mar. 10, 2001), available at <http://www.bmj.com/content/322/7286/575.3?tab=related>.

¹²⁴ JAMES V. LAVERY, CHRISTINE GRADY, ELIZABETH R. WAHL, EZEKIEL J. EMANUEL, *ETHICAL ISSUES IN INTERNATIONAL BIOMEDICAL RESEARCH*, (A Casebook, eds., 153, Oxford University Press, 2007).

¹²⁵ Charatan, *supra* note 122.

¹²⁶ Lavery, et al., *supra* note 123.

¹²⁷ *Id.*

provider, who would then administer either air suffused with Surfaxin or air without any drug.¹²⁸ The endpoints for the proposed study were number of deaths from any cause by day 28 and deaths due to direct or indirect complications of RDS.¹²⁹ There were no specific plans to market Surfactant in Latin America, while the United States and Europe were the principal target market for the drug.¹³⁰ The sponsor proposed to make Surfaxin available at a very low cost in the countries of the proposed study, if proved effective. However, there was no firm agreement reached on the negotiation.¹³¹ According to Dr. Sidney Wolfe¹³² the infants in the placebo arm are being used by Discovery Laboratories “for reasons having to do with corporate bottom lines in order to get their drug approved.”¹³³

Despite the Nigerian Trovan Study experience, researchers continue to throw caution to the winds by involving human subjects in research that is greater than minimal risk. If the Proposed Bolivia Study had not been halted, it would have been another exploitation of vulnerable populations that may have resulted in unnecessary deaths.

III. Analysis of Ethical Issues Arising from the Nigerian Trovan Study

A. Informed Consent and Socio-Cultural Factors

Informed consent is the basis of the relationship between patients and physicians and in the case of clinical research, between the subjects and the researcher.¹³⁴ Both the international guidelines¹³⁵ and the United States regulations on human subject research¹³⁶ all require the voluntary informed consent of the subjects. The Nuremberg Code requires absolute voluntary

¹²⁸ *Id.*

¹²⁹ *Id.*

¹³⁰ *Id.*

¹³¹ *Id.* at 154.

¹³² The Director of Public Citizen’s health research group.

¹³³ Charatan, *supra* note 122.

¹³⁴ The investigators and sponsors of the research also owe a duty to obtain voluntary informed consent from the subjects.

¹³⁵ The Nuremberg Code, the Declaration of Helsinki, the ICCPR, the CIOMS Guidelines, and the Belmont Report.

¹³⁶ The Common Rule, Title 45 C.F.R. Part 46 and the FDA regulation, Title 21 C.F.R. Part 50.

consent from subjects.¹³⁷ It approaches voluntary consent through a moral approach because the society regards people are self-autonomous, while the Declaration of Helsinki and the CIOMS Guidelines approach voluntary consent from the doctor-patient and the patient and surrounding circumstances respectively.¹³⁸

The Nuremberg Code does not address socio-cultural factors affecting the doctrine of informed consent. The Declaration on the other hand, did not specifically addressed socio-cultural factors but it allows physicians to follow research subjects' national laws and standards.¹³⁹ The CIOMS Guidelines recognizes socio-cultural factors on informed consent but provides that permission of a community leader or other authority may not be substituted for individual informed consent.¹⁴⁰ In many developing countries, like Nigeria for example, it is customary in some communities for community leaders to give consent on behalf of its members. In some patriarchal cultures, females are prohibited from making personal important decisions for themselves or on behalf of their children.¹⁴¹ Nigeria as a country is a multi-cultural, multi-ethnic, and multi-religious nation¹⁴² and the perceptions on health issues are strongly influenced by these factors as well as the belief in the extended family system.¹⁴³ Northern Nigeria has a strong centrally-controlled feudal system that has strong influence on the decision to undertake treatment, which sometimes could be detrimental to the patient.

¹³⁷ The Nuremberg Code, *supra* note 15, at art.1.

¹³⁸ Carr, *supra* note 2, at 31.

¹³⁹ The Declaration, *supra* note 21, Principle 10.

¹⁴⁰ The CIOMS Guidelines, *supra* note 36, Commentary on Guideline 4.

¹⁴¹ Carr, *supra* note 2, at 32.

¹⁴² Lawal Y Z, Garba E S, Ogirima M O, Dahiru I L, Maitama M I, Abubakar K. *The Doctrine of Informed Consent in Surgical Practice*. Ann Afr Med [series online] 2011 [cited 2013 Aug. 28]; 10:1-5, available at <http://www.annalsafmed.org/text.asp?2011/10/1/1/76558>.

¹⁴³ *Id.*

In such culture, “community consent clashes with the Declaration’s policy that individuals personally volunteer for the experimental procedure.”¹⁴⁴ As David Carr noted, if a country does not codify the community consent concept within its laws, researchers would be left with no guidance to deal with communities that traditionally allow community consent.¹⁴⁵ In Pfizer’s Trovan case however, conducting an experimental research along with providing charitable medical care to sick people may lead to misconception by the patients who may not necessarily volunteer for the research but for the treatment.¹⁴⁶ Under such circumstance, where medical treatment is being rendered by charitable organizations, it is easy for a subject to mistake the experimental research for treatment and thereby “disposing of the need for researchers to obtain consent.”¹⁴⁷

B. Lack of Informed Consent and Potential for Exploitation of Vulnerable Research

Subjects

The heart of the issue in the Nigerian Trovan Study was that Pfizer allegedly did not obtain informed consent of the subjects in accordance with international guidelines and the FDA regulations.¹⁴⁸ The Nigerian Trovan Study involved pharmaceutical research and thus the FDA has jurisdiction over the Trovan clinical study.¹⁴⁹ The Nigerian Trovan Study arguably violated Title 21 C.F.R. § 50.20 which requires that researchers or investigators obtain informed consent from the subject or the subject’s legally authorized representative, provide information in language understandable to the subject or the representative, provide subject or the representative enough opportunity to consider whether or not to participate in the research, as well as minimize

¹⁴⁴ Carr, *supra* note 2 at 34.

¹⁴⁵ Carr, *supra* note 2 at 33.

¹⁴⁶ Carr, *supra* note 2 at 34.

¹⁴⁷ *Id.*

¹⁴⁸ Abdullahi v. Pfizer, Inc., *supra* note 117 at 169. *See also* 21 C.F.R. § § 50.20 and 50.55 (2013), CIOMS Guidelines; The Declaration of Helsinki and The Nuremberg Code.

¹⁴⁹ Title 21 C.F.R. § 50 on Protection of Human Subject and Title 21 C.F.R. § 56 on Institutional Review Boards.

the possibility of coercion or undue influence.¹⁵⁰ The subjects claimed that neither they nor their parents were told that they were part of a clinical trial.¹⁵¹ Also, a Nigerian laboratory technician was reported to have corroborated this fact, saying they “did not know if it was research or not,” “they just knew they were sick.”¹⁵² This arguably was a contravention of Article 7 of ICCPR with regards to informed consent of human subject research which prohibits nonconsensual medical or scientific human experimentation.¹⁵³ Local nurses were said to have explained the research to the families in their native language,¹⁵⁴ but did not provide full translation of the consent form.¹⁵⁵ Thus, there were significant flaws with adequacy of the informed consent sought and obtained from subjects.

The Declaration of Helsinki,¹⁵⁶ the CIOMS Guidelines¹⁵⁷ and the FDA regulations¹⁵⁸ all require documentation of informed consent. 21 C.F.R. section 50.27 states “informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of consent. A copy shall be given to the person signing the form.”¹⁵⁹ In this case, Pfizer could not produce any consent form documenting the informed consent procedure as required by both international

¹⁵⁰ Title 21 C.F.R. § 50.20 (2013).

¹⁵¹ *Abdullahi I*, *supra* note 93 at *1.

¹⁵² Joe Stephens, *Where Profits and Lives Hang in Balance*, Washington Post, Dec. 17, 2000, available at <http://www.washingtonpost.com/wp-dyn/content/article/2007/07/02/AR2007070201255.html>.

¹⁵³ ICCPR *supra* note 46.

¹⁵⁴ *Id.*

¹⁵⁵ Stephens, *supra* note 151. It should be noted that Kano where the study was conducted is one of the northern states in Nigeria, whose residents are mainly Hausas and Fulanis who are mostly illiterates and could not have been able to comprehend the issue of informed consent compared to their literate counterparts from southern Nigeria who are mainly Ibos and Yorubas. Based on this fact, it is impossible to know whether the local nurses adequately interpreted the consent procedure and made it clear to the subjects and their parents that they are being used in research.

¹⁵⁶ The Declaration, *supra* note 21, Principle 26.

¹⁵⁷ CIOMS Guidelines, *supra* note 36, Guideline 4 Commentary.

¹⁵⁸ Title 21 C.F.R. § 50.27 (2013).

¹⁵⁹ Title 21 C.F.R. § 50.27(a) (2013).

guidelines and FDA regulations.¹⁶⁰ Even though Pfizer asserted to have obtained verbal consent and that local nurses spoke with the families, the company admitted that no witnesses attested to the verbal consent given.¹⁶¹

This situation and other factors¹⁶² surrounding it, is a clear case of exploitation of vulnerable population; the subjects involved were poor sick children whose parents or guardians are illiterates who were looking for treatment to alleviate their health conditions. The CIOMS Guidelines categorizes children, the poor and illiterates as a vulnerable population and requires special justification when these groups are invited to serve as research subjects, “and if they are selected, the means of protection of their rights and welfare must be strictly applied.”¹⁶³ The Nigerian Trovan Study clearly contravenes the CIOMS Guidelines on this issue, because Pfizer failed to obtain consent from the subjects’ parents or guardians and to protect their welfare.¹⁶⁴ The Declaration also requires caution when research involves vulnerable populations and that research is only justified if it is responsive to the health needs of the group.¹⁶⁵ Arguably, Pfizer exploited the subjects’ situation of need (outbreak of meningitis and need for treatment) and experimented on them, when they were merely looking to cure their disease.¹⁶⁶ Pfizer administered Trovan orally to the sick children solely to get FDA’s approval of its application¹⁶⁷ and also failed to protect the welfare of the sick children who did not respond well to Trovan as they were not switched to Ceftriaxone.¹⁶⁸ Moreover, the subjects’ parents are illiterates who could not speak or understand English language; they simply believed their children were

¹⁶⁰ Stephens, *supra* note 151.

¹⁶¹ Postal et al., *supra* note 119, at 18-19.

¹⁶² 21 C.F.R. § § 50.20 and 50.55 (2013), CIOMS Guidelines, *supra* note 36, The Declaration, *supra* note 21, and The Nuremberg Code, *supra* note 15.

¹⁶³ CIOMS Guidelines, *supra* note 36, Guideline 13. *See also* commentary to Guideline 13.

¹⁶⁴ Abdullahi I, *supra* note 93 at *1.

¹⁶⁵ The Declaration, *supra* note 21, Principles 19 and 20.

¹⁶⁶ Stephens, *supra* note 151.

¹⁶⁷ Abdullahi I, *supra* note 93 at *2.

¹⁶⁸ *Id.*

receiving effective treatment for meningitis rather than being enrolled in an experimental research.¹⁶⁹

If the “proposed Bolivia Study” had been allowed to see the light of the day, it would have been another case of wrongful exploitation of vulnerable population. It would have been a case of medical experimentation for profit carried out in poor countries and on sick children. The “proposed Bolivia Study” could have met the requirement for informed consent but would have been a case of exploitation as there was no plan to make the drug available in the host country because it would have been expensive and unaffordable.¹⁷⁰

The main purpose of the Trovan study performed by Pfizer was to gain approval for marketing of the drug in the United States can be construed as a premeditated case of exploitation of vulnerable population as they were not meant to benefit from the research.¹⁷¹ In the Bolivian case, the intention to use placebo when there were four approved surfactants in use in the United States contravenes the Declaration of Helsinki, which states “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s)...”¹⁷² This research would have caused unnecessary deaths in the placebo arm.

C. Lack of Risk and Benefit Information

Subjects in the Nigerian Trovan Study claimed Pfizer never informed them of the potential risks involved – a situation which would have been deemed unethical in the US, leaving eleven children dead and several others disabled.¹⁷³ The FDA’s regulations regarding involving children in minimal risk research¹⁷⁴ was not adhered to by Pfizer. The study deviated from the

¹⁶⁹ Nwabueze, *supra* note 9 at 98.

¹⁷⁰ Lavery, et al., *supra* note 123.

¹⁷¹ Stephens, *supra* note 151.

¹⁷² The Declaration, *supra* note 21, Principle 33.

¹⁷³ *Abdullahi I*, *supra* note 93 at *2.

¹⁷⁴ 21 C.F.R. § 50.51

standard of care for meningitis by administering Trovan orally to the Nigerian children, whereas in the United States and other developed countries, the standard of care is intravenous antibiotics.¹⁷⁵ Furthermore, Pfizer administered Trovan to the Nigerian children despite animal studies indicating that Trovan use may be associated with bone deformities, joint diseases and liver injury.¹⁷⁶

Arguably, Pfizer violated the principle of The Declaration of Helsinki on risks, burdens and benefits assessment which states that “medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects ... and must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.”¹⁷⁷ Since prior animal studies linked Trovan’s use to increases morbidity and perhaps mortality from liver injury, joint diseases and bone diseases, the burdens of the Nigerian Trovan Study is foreseeable and clearly outweigh the benefits. Therefore, Pfizer should not have used this medication or at least communicated these risks explicitly to the subjects’ parents or guardians.

D. Lack of Independent Ethical Review

The Declaration of Helsinki, the CIOMS Guidelines and the FDA’s regulations require that an ethics review committee review and approve research protocols prior to conducting a medical research involving human subject.¹⁷⁸ The case is different in Nigeria and many other African countries where there is neither state nor federal formal regulatory system of ethics

¹⁷⁵ Macklin, *supra* note 91 at 476.

¹⁷⁶ Wollensack, *supra* note 7 at 756.

¹⁷⁷ The Declaration, *supra* note 21, Principles 16 and 17.

¹⁷⁸ The Declaration, *supra* note 21, Principle 23, CIOMS Guidelines, *supra* note 36, Guideline 2, and 21 C.F.R. § 50.50 (2013).

review or research guidelines issued by the country's medical research institutions.¹⁷⁹ Nwabueze noted that the "regulatory deficiency was probably responsible for the Trovan tragedy in Nigeria."¹⁸⁰ It has been reported that in a survey conducted by the National Bioethics Advisory Committee, one-fourth of all clinical trials conducted in foreign countries went through no ethical review at all.¹⁸¹

Pfizer asserted that the Nigerian Trovan Study was approved by a Nigerian ethics board;¹⁸² but investigation revealed that at the time of the study, there was no ethics review board at the hospital where the study was conducted.¹⁸³ In response to a 1997 FDA's audit investigation, Dr. Dutse, Nigerian lead investigator "in charge of local aspects of the study admitted that his office falsified document stating approval of the study by an ethics review board".¹⁸⁴ According to an FDA official, "a knowing submission of false documents to a US government agency is a violation of federal law."¹⁸⁵ Even though the FDA has jurisdiction over "clinical research and protection of child subjects, there are no provisions explicitly protecting against fraud."¹⁸⁶

While research is encouraged for advancement of health and prevention of diseases, market forces and lack of concern for distributive justice (access to the intervention if beneficial) sometimes can lead to exploitation especially in developing countries with little or no basic healthcare, large number of naïve, poor, and illiterate human subjects. More stringent

¹⁷⁹ Nwabueze, *supra* note 9, at 102.

¹⁸⁰ *Id.*

¹⁸¹ Adam H. Laughton, *Somewhere to Run, Somewhere to Hide?: International Regulation on Human Subject Experimentation*, 18 DUKE J. COMP. & INT'L L. 181, 210 (2007).

¹⁸² Stephens, *supra* note 151.

¹⁸³ Macklin, *supra* note 91 at 477. *See also* Abdullahi v. Pfizer, Inc., *supra* note 117 at 169.

¹⁸⁴ Macklin, *supra* note 91, at 477.

¹⁸⁵ *Id.*, (citing J. Stephens, *Doctors Say Trial's Approval Was Backdated*. WASHINGTON POST January 16, 2001: A01).

¹⁸⁶ Postal, et al., *supra* note 119 at 20.

safeguards and protections could be put in place, specifically to address each of the factors that could lead to exploitation.

IV. Current Changes to Foreign Research Regulations and Suggestions for Improvement.

A. Impact of Pfizer’s Trovan Study in Nigeria on Foreign Research Regulations

In the aftermath of the Nigerian Trovan Study, there have been a lot of commentaries and articles written condemning the unethical conduct and abuses involved. In response, there have been amendments to both international guidelines and the United States’ regulations on human subject research in developing countries.

i. The Declaration of Helsinki

The Declaration of Helsinki has been revised multiple times and there have been two notes of clarification added.¹⁸⁷ The 2013 Declaration¹⁸⁸ includes several subsections which enhance and provide clarity on some specific issues; thus making the 2013 Declaration “a better and more important authority ... providing guidance on conducting medical research involving humans.”¹⁸⁹ The 2013 Declaration of Helsinki addresses some of the ethical issues in biomedical research in developing countries. It identifies and encourages researchers to pay attention to socio-cultural factors that may affect obtaining voluntary informed consent.¹⁹⁰ For example, in some cultures, community leaders or heads of household serve as additional layer of protection that researchers must pass through before obtaining informed consent from potential subjects.¹⁹¹

¹⁸⁷ The Declaration of Helsinki, amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, 59th WMA General Assembly, Seoul, Korea, October 2008, 64th WMA General Assembly, Fortaleza, Brazil, October 2013 [hereinafter the Declaration of Helsinki 2013] with notes of clarification added by the 53rd WMA General Assembly, Washington, DC, USA, October 2002 and 55th WMA General Assembly, Tokyo, Japan, October 2004.

¹⁸⁸ The Declaration of Helsinki amended by 64th WMA General Assembly, Fortaleza, Brazil, October 2013 [hereinafter the 2013 Declaration].

¹⁸⁹ Paul Ndebele, *The Declaration of Helsinki, 50 Years Later*, JAMA Published online October 19 (2013), at E2.

¹⁹⁰ The 2013 Declaration, *supra* note 188, Principle 25 acknowledges the need to respect culture and community norms as part of the research process.

¹⁹¹ Ndebele, *supra* note 189.

It also encourages compensation and treatment of subjects when injury occurs during a study,¹⁹² as well as subjects' access to proven interventions or drugs after the study.¹⁹³ It discourages the use of placebo unless where proven interventions are non-existent.¹⁹⁴ Finally it emphasizes the importance of ethics committee's review of study protocols, monitoring ongoing studies for adverse events and the need to terminate a study if safety concern arises.¹⁹⁵

With the Declaration of Helsinki 2013 specifically addressing research issues pertaining to research in developing countries, its influence in serving as an important international document to stakeholders in limited-resource settings should increase.¹⁹⁶ And for research sponsors, ethics committees, and subjects, the current version of the Declaration of Helsinki should be empowering given its emphasis on issues of justice.¹⁹⁷

ii. The Food and Drug Administration (FDA) Policies on Foreign Research

The FDA has likewise modified its regulations on human subject research in foreign countries following the devastation caused by the Nigerian Trovan Study. The FDA on April 28, 2008 promulgated regulations on the acceptance of foreign clinical studies not conducted under an investigational new drug application ("The 2008 Rule").¹⁹⁸ The 2008 Rule has been said to be part of the FDA's effort to issue more binding regulations rather than industry guidance regarding clinical trials.¹⁹⁹ The 2008 Rule was promulgated to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies as well as the quality and integrity of the resulting data. The 2008 Rule requires that foreign clinical studies for marketing applications must be conducted in accordance with good clinical practice (GCP); include a review and

¹⁹² The 2013 Declaration, *supra* note 188, Principle 15.

¹⁹³ *Id.*, Principle 34.

¹⁹⁴ *Id.*, Principles 33 and 37.

¹⁹⁵ *Id.*, Principle 23

¹⁹⁶ Ndebele, *supra* note 189.

¹⁹⁷ *Id.*

¹⁹⁸ 73 Fed. Reg. 22,800.

¹⁹⁹ Postal, et al., *supra* note 119.

approval by an independent ethics committee (IEC) and written informed consent from subjects.²⁰⁰

a. Informed Consent of Subjects

The 2008 Rule added additional layer of protections to human subjects' research on the issue of informed consent. It makes it mandatory for sponsor or applicant to disclose to the FDA a description of how and when informed consent was obtained from the subjects,²⁰¹ such as a written document that is witnessed, signed and dated from the research subject. However, informed consent of the subject is not required in certain life-threatening circumstances²⁰² such as when a lifesaving compassionate medical treatment or intervention is urgently needed and the clinician is unable to communicate with either the subject because of coma or his/her legal representative because of unavailability, or when there is no alternative method of therapy that provides equal or greater likelihood of saving the subject's life.²⁰³ In such situations, it is the responsibility of the IEC to conduct its review before the study begins, make a finding that obtaining informed consent is not feasible, and either find that the conditions present are consistent with those described in section 50.23 or section 50.24(a) of 21 C.F.R., or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects.²⁰⁴

b. Review and Approval by Independent Ethics Committee (IEC)

²⁰⁰ U.S. Dept. of Health and Human Services, Food and Drug administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Office of Good Clinical Practice, *Guidance for Industry and FDA Staff FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions*, at 1, March 2012, available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm294729.pdf> (last visited Dec. 7, 2013).

²⁰¹ 73 Fed. Reg., at 22,809.

²⁰² *Id.* at 22,806.

²⁰³ *Id.* at 22,801.

²⁰⁴ *Id.* at 22,816.

The 2008 Rule defined an Independent Ethics Committee as “a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.”²⁰⁵ It makes it mandatory that foreign clinical trials be reviewed and approved by an Independent Ethics Committee,²⁰⁶ and clarifies that an IRB is a type of IEC.²⁰⁷

The 2008 Rule requires the sponsor or applicant to submit information, including the name and address of the IEC that reviewed the study; a statement of the IEC’s qualification in accordance to section 312.3; maintenance of supporting records containing the names and qualifications of the IEC members must be kept and be available for the agency’s review; submission of the names and qualifications of the IEC members that reviewed the study and a summary of the IEC’s decision to modify or approve the study or a favorable opinion of the study.²⁰⁸

c. Good Clinical Practice

The 2008 Rule defines Good Clinical Practice “as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.”²⁰⁹ The 2008 Rule also requires that GCP include oversight by an IEC and obtain informed consent of subjects.²¹⁰ The 2008 Rule clarifies the limited circumstances in which GCP would not require informed consent.²¹¹ In such life-threatening situations, the IEC has a responsibility to review the study, make a finding that

²⁰⁵ *Id.* at 22,805.

²⁰⁶ *Id.* at 22,800.

²⁰⁷ *Id.* at 22,805.

²⁰⁸ *Id.* at 22,802

²⁰⁹ *Id.* at 22806.

²¹⁰ *Id.*

²¹¹ *Id.*

obtaining informed consent was not feasible, and that the conditions present are consistent with those described in section 50.23 or 50.24(a) of Title 21 C.F.R.²¹² The purpose of the GCP requirement for non-IND foreign clinical studies is to help ensure proper conduct of trials, protect data quality and integrity.²¹³

The United States Department of Health and Human Services (DHHS) in its bid to offer more protection for human subject research is in the process of amending the current 2008 Rule. The proposed changes under consideration can be found in an Advance Notice of Proposed Rulemaking (“ANPRM”),²¹⁴ and are designed to strengthen protections for human research subjects. These proposed changes include but not limited to: creation of a single website for the electronic reporting of all events and to harmonize the reporting requirements across agencies; provision of specificity on how consent forms should be written to contain all necessary information that would facilitate participant’s quality decision to participate or not in a study. Also the ANPRM proposes to extend federal regulations protection to all studies involving human subjects conducted in the U.S. regardless of funding source.²¹⁵

Even though the ANPRM does not include studies or trial conducted in foreign countries, it could be argued that since most of these studies fall under the supervision of the FDA, the changes regarding having a single database for reporting all events and revision to the consent form would apply to foreign research involving human subjects. With a single database for reporting all clinical trial events, it would foster transparency and minimizes exploitation of research subjects. Most especially, a shorter consent form that is more readily understood and

²¹² *Id.* at 22,806.

²¹³ *Id.* at 22,801.

²¹⁴ Advance Notice of Proposed Rulemaking (ANPRM), *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*, published in the July 25 Federal Register.

²¹⁵ See Regulatory Changes in ANPRM, available at <http://www.hhs.gov/ohrp/humansubjects/anprmchangeable.html> (last visited Dec. 7, 2013).

less confusing would enhance the quality of decisions of research subjects in developing countries.

B. Suggestions for Improvement of Informed Consent Process in Developing Countries

The informed consent doctrine continues to be an integral part of research whether conducted locally or internationally. Binding regulations ratified and enforced by all nations involved in human subject research in developing countries are urgently needed to protect the right, dignity and safety of subjects. The elements of informed consent and independent ethics review board needs to be strengthened and enforced globally with high standard for international research in developing countries. Most times, the host country do not benefit from a new drug or intervention due to poverty and inadequate health care funding by host government. Therefore, regulations should promote equitable distribution of burdens and benefits for research conducted in developing countries by making proven intervention available to research subjects and the host countries.

Human subjects' research continues to be an important aspect of medical advancement; however, private companies see this as more of economic benefit than medical and knowledge venture. Children are precious, innocent and very vulnerable and should not be subjected to inhumane and degrading treatment all in the name of advancing medical knowledge, treatment or cure for diseases. Children deserve self-respect like every other person, and should not be exploited simply by origin of their birth or because they are unable to make decisions as to what should be done to their bodies. Even when parents volunteer their children for medical experimentation, it should not be seen as a means of exploitation, they are individuals and should never be treated as "objects" or "tools" for achieving scientific or medical knowledge. Echoing the words of Francis Payton Rous, editor of the *Journal of Experimental Medicine*, in 1941 he

stated in a letter rejecting a manuscript from a physician that “the inoculation of a twelve month old infant with herpes ... was an abuse of power, an infringement of the rights of an individual, and not excusable because the illness which followed had implications for science.”²¹⁶ The fact that “a child was ‘offered as a volunteer’ – whatever that may mean – does not palliate the action.”²¹⁷

Considering the controversy and several litigations surrounding the Pfizer Trovan Nigerian Study on informed consent, this paper offers the following suggestions for improving informed consent process in developing countries, particularly for research involving children as subjects. The informed consent form must be approved by the host country’s independent ethics review committee and the federal health agency charged with regulating and controlling the manufacture, importation, distribution, sale and use of drugs and medical devices. Informed consent must be voluntary and the consent form must be written in simple easily comprehensive words (native language where applicable). There should be a proper and accurate documentation of the informed consent process; a copy of the signed consent form must be kept in the research file and must also be given to the research subject or legal representative. In cases where it is not possible to provide a full and accurate translation of the consent form in the applicable native language, services of certified local medical interpreter should be employed and proper documentation must be kept in the research file. Furthermore, investigators and researchers should be specifically required to provide adequate clarification between experimental research and charitable aid.²¹⁸

Conclusion

²¹⁶ LORI B. ANDREWS, ET AL., GENETICS: ETHICS, LAW AND POLICY, 3^D Ed., 114, WEST (2010).

²¹⁷ *Id.*

²¹⁸ Carr, *supra* note 2 at 52.

International biomedical research in developing countries continues to be faced by ethical challenges because of a multitude of factors such as sociocultural differences, literacy rate, wealth, access to basic health care, politics and market forces driving big pharmaceutical companies in developed countries. The risk benefit ratio of potential harm to subjects must be strongly considered to the knowledge gained from such research. Sometimes these risks-benefits assessment are not done especially when researches are driven by market force from private and multinational pharmaceutical companies that eventually lead to injustice and exploitation of vulnerable populations; this is the case in the Nigerian and the proposed Bolivian studies.