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FORM OVER SUBSTANCE: THE INADEQUACY OF INFORMED CONSENT AND ETHICAL REVIEW FOR THAI INJECTION DRUG USERS ENROLLED IN HIV VACCINE TRIALS

Joan M. Doherty[†]

Abstract: Acquired Immune Deficiency Syndrome (“AIDS”) has emerged as a health issue of global significance, and clinical research on Human Immunodeficiency Virus (“HIV”) and AIDS has become increasingly international in scope. A clinical trial of a vaccine designed to prevent the spread of the HIV raises important legal and ethical questions because injection drug users who were believed to be unsuitable subjects for study in the United States were singled out for research in Thailand. The protections for human subjects must not be compromised when U.S. pharmaceutical companies conduct research abroad, particularly where clinical trials are conducted in vulnerable populations.

U.S. regulations, as well as international declarations and guidelines, require two primary protections for research subjects: individual voluntary informed consent, and prior review of proposed research by an independent ethical review committee. Ethical review committees should gauge the adequacy of informed consent by the substance of the information communicated between researcher and participant, and should not be satisfied with a mere signature on a consent form. The recent clinical trial of HIV vaccines in the United States and Thailand highlights the gaps and weaknesses in the current system of protections for human subjects. Members of the committees that reviewed the protocols for the AIDSVAX vaccine failed to properly consider the vulnerability of the subject population and the implications for informed consent.

Countries that host research sponsors, as well as countries that host research volunteers, must share the responsibility of protecting human subjects. To strengthen the protections for human subjects, Thailand should enact comprehensive national legislation, and existing legislative protections in the United States should be expanded to reflect the increasingly international scope of biomedical research. As a case study, the AIDSVAX clinical trials can provide useful information for planning more equitable HIV vaccine trials in the future.

I. INTRODUCTION

Acquired Immune Deficiency Syndrome (“AIDS”) has become a health epidemic that no community, nation, or continent can ignore. AIDS is the “first modern infectious disease to strike the developed and developing world simultaneously and to give both a large stake in finding a cure.”¹ As biomedical research becomes increasingly international in scope, clinical trials often involve several nations that are socially, politically, and

[†] The author would like to thank Professor Anna C. Mastroianni and the Editorial and Production Staff of the *Pacific Rim Law & Policy Journal* for their assistance throughout the writing process. Any errors or omissions are the author’s own.

¹ David J. Rothman, *The Shame of Medical Research*, N.Y. REV. OF BOOKS, Nov. 30, 2000, at 60-64.

economically distinct.² When clinical research is conducted in both developed and developing nations, a system of protections is necessary to ensure that the treatment of human subjects does not vary with the location of the research.

Federal regulations in the United States and most international guidelines require two fundamental protections for research subjects: (1) individual voluntary informed consent, and (2) prior review of proposed research by an independent ethical review committee.³ These protections are necessary to ensure that the autonomy of research participants is respected, that volunteers consider the risks and benefits of participation, and that the benefits and burdens of research are equitably distributed.⁴

A recent clinical trial of a vaccine designed to prevent the spread of Human Immunodeficiency Virus (“HIV”) raises important legal and ethical questions because injection drug users who were believed to be unsuitable subjects for study in the United States were singled out for research in Thailand.⁵ At the time of the research, injection drug users were subjected to coercive government programs in Thailand that did not exist in the United States.⁶ Given the study populations and social conditions in Thailand at the time of the study, it would have been more appropriate to conduct the research solely in the United States. When protocol review committees slavishly adhere to regulatory forms without properly considering substantive ethical issues and the local research context, inappropriate research may proceed. Approval by ethical review committees of HIV vaccine trials in Thailand represents one example of the form of legal and ethical analysis prevailing over substance.

If the United States and Thailand continue to collaborate in the search for an HIV vaccine, the protections for human subjects that are enforced in the United States must be equally robust when applied in Thailand. Part II of this Comment provides background information on the HIV clinical trials, and considers the ethical and legal implications of international biomedical research. Part III argues that U.S. regulations provide one source of protection to human subjects in Thailand, given the absence of Thai

² See Esther Chang, *Fitting a Square Peg into a Round Hole?: Imposing Informed Consent and Post-trial Obligations on United States Sponsored Clinical Trials in Developing Countries*, 11 S. CAL. INTERDISC. L.J. 339, 340 (2002).

³ Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANNALS OF INTERNAL MED. 282, 282 (2004).

⁴ See Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,192, 23,293-94 (Apr. 18, 1979), available at <http://www.nihtraining.com/ohrsite/guidelines/belmont.html> [hereinafter Belmont Report].

⁵ See discussion *infra* Part II.A.

⁶ See discussion *infra* Part IV.A.3.

legislation. However, Part IV illustrates that in the case of the HIV vaccine clinical trials in Thailand, U.S. regulations governing informed consent were ineffectively applied. Part V suggests several approaches to strengthen existing protections for human subjects in future clinical trials.

II. INTERNATIONAL VACCINE TRIALS ADVANCE THE FIGHT AGAINST THE HIV/AIDS EPIDEMIC BUT ALSO HIGHLIGHT RESOURCE DISPARITIES

Vaccines represent one possible way to curb the spread of HIV/AIDS. Most vaccines currently being explored in the context of HIV are preventive vaccines, which teach the body to recognize and defend itself against the viruses that cause the disease.⁷ Preventive vaccines cannot cure someone who has HIV or AIDS, but may prevent infection or slow the progression of HIV to AIDS.⁸ Clinical trials of vaccines are research studies in which new therapies for AIDS and HIV infection are tested in humans to assess whether the drugs or vaccines actually work as intended.⁹ Clinical trials of HIV vaccines progress through three phases. After a vaccine is shown to be safe in humans at a particular dosage level (Phase I), and initial evidence shows that it might be effective (Phase II), it may proceed to large-scale efficacy trials (Phase III).¹⁰

This Comment focuses on the challenges of conducting a Phase III HIV vaccine clinical trial. First, HIV clinical trials require healthy volunteers. In the typical research scenario, the subjects recruited for drug trials are directly interested in the outcome of the trial because they already have the disease the drug is designed to treat.¹¹ Yet in order to know if a vaccine works, the subjects recruited for clinical trials must be healthy individuals who may be at risk for HIV at some future time.¹² A second challenge for Phase III vaccine trials is the large number of volunteers needed. While Phases I and II of vaccine testing require only several

⁷ See INTERNATIONAL AIDS VACCINE INITIATIVE, *Questions and Answers About Vaccines & AIDS* (2005), <http://www.iavi.org/viewpage.cfm?aid=33>.

⁸ *Id.*

⁹ See AIDSINFO, U.S. Department of Health and Human Services, *What is an AIDS Clinical Trial?*, (2005), <http://www.aidsinfo.nih.gov/other/whatisct.pdf>.

¹⁰ See Carol Rados, *Inside Clinical Trials: Testing Medical Products in People*, FDA CONSUMER, Sept.-Oct. 2003, available at http://www.fda.gov/fdac/features/2003/503_trial.html. In the United States, a new vaccine must pass through four stages before it will be approved and licensed by the FDA. Testing vaccines in humans can only be undertaken after animal testing demonstrates that the vaccine is sufficiently safe, as determined by the FDA. Jennifer Berman, *Using the Doctrine of Informed Consent to Improve HIV Vaccine Access in the Post-TRIPS Era*, 22 WIS. INT'L L. J. 273, 283 (2004).

¹¹ See CHRISTINE GRADY, *THE SEARCH FOR AN AIDS VACCINE: ETHICAL ISSUES IN THE DEVELOPMENT AND TESTING OF A PREVENTIVE HIV VACCINE* 64-65 (1995).

¹² *Id.* at 65.

hundred volunteers, Phase III trials test thousands of healthy participants for efficacy and side effects in order to reveal the less common effects of the vaccine.¹³ In particular, HIV vaccine trials require larger numbers of participants because only a small number of those vaccinated will ever be exposed to and contract HIV, even if no effective vaccine is given.¹⁴ In other words, for the clinical trials to be scientifically meaningful, the research subjects must not only be healthy, but must also have a relatively high risk of acquiring HIV.¹⁵ Phase III vaccine trials therefore pose the challenge of recruiting and maintaining a large number of healthy but at-risk volunteers.

A. *Participation Criteria for the VaxGen HIV Clinical Trials in Thailand Differed from the Criteria in the United States*

VaxGen, a biomedical research company based in the United States, developed an HIV vaccine called "AIDSVAX."¹⁶ VaxGen also funded most aspects of the clinical trials to test the HIV vaccine.¹⁷ AIDSVAX was the first experimental vaccine to be approved by the Food and Drug Administration ("FDA") for large-scale testing,¹⁸ and Thailand was the first developing nation to host a large human trial of an experimental HIV vaccine.¹⁹ The study began in the United States in June 1998,²⁰ and in Bangkok, Thailand in March 1999.²¹ The Bangkok Metropolitan Administration (BMA) led the Thai trial, in conjunction with VaxGen, the Mahidol University Faculty of Tropical Medicine in Bangkok, and the HIV/AIDS Collaboration (a research collaborative between the Thai Ministry of Public Health and the Centers for Disease Control and Prevention).²²

Although the vaccine trials in the United States and Thailand tested similar versions of the AIDSVAX vaccine and were funded by the same company (VaxGen), there were significant differences in the criteria for

¹³ See Rados, *supra* note 10.

¹⁴ See Grady, *supra* note 11.

¹⁵ *Id.* at 121.

¹⁶ VaxGen is based in California. AIDSINFO, U.S. Department of Health and Human Services, *Questions and Answers on the Thailand Phase III Vaccine Study and CDC's Collaboration* (1999), http://aidsinfo.nih.gov/aprs/aprs_press.asp?an=A00487 [hereinafter *AIDSINFO Phase III*].

¹⁷ *Id.* "There's no guarantee the vaccine will work, and many U.S. scientists are highly skeptical because it's based on a concept that the National Institutes of Health shelved in 1994." *FDA Allows Large-Scale Test of AIDS Vaccine*, THE COLUMBUS DISPATCH (Ohio), June 4, 1998, at 5A.

¹⁸ See Bill Hutchinson, *Firm Gets OK to Test AIDS Drug*, DAILY NEWS (New York), June 4, 1998, at 2.

¹⁹ See Peter Alford, *Thais to Test HIV Vaccine*, THE AUSTRALIAN, Feb. 11, 1999, at 7.

²⁰ AIDSINFO *Phase III*, *supra* note 16.

²¹ Aphaluck Bhatiasavi, *VaxGen to Stop Funding of Vaccine Trial*, BANGKOK POST, July 2, 2003.

²² AIDSINFO *Phase III*, *supra* note 16.

participation. The population of 5,000 research subjects recruited in the United States was comprised of non-monogamous gay men or heterosexuals.²³ Injection drug users were excluded from participating in the U.S. trials.²⁴ Those who designed the study believed it would be too difficult to follow a population of injection drug users in the United States.²⁵ In contrast, the Thai version of the study was conducted exclusively among 2,500 uninfected injection drug users attending 17 drug treatment clinics in Bangkok.²⁶ In other words, while the use of injection drugs was grounds for exclusion from the U.S. trials, it was a requirement for participation in the Thai trials.

For the purposes of this discussion, the results of the AIDSVAX vaccine trial are of little significance. The trials conducted in both the United States and Thailand ultimately showed that neither form of the vaccine effectively prevented HIV infection among study participants.²⁷ However, the vaccine trials provide an important context for examining the legal and ethical issues raised by international research.

As evidenced by the selection criteria, researchers generally follow populations that are considered to be at high risk of exposure due to sexual contact or injection drug use. While health officials are obligated to ensure that all participants benefit from known prevention methods—such as the use of condoms and clean syringes—the studies will only be informative if

²³ See Elizabeth Neus, *U.S. Clears Test of AIDS Vaccine*, CHICAGO SUN-TIMES, June 4, 1998, at 22.

²⁴ CLINICALTRIALS.GOV, NATIONAL INSTITUTES OF HEALTH, *Effectiveness of an HIV Vaccine in HIV-Negative Adults in North America Who Are at Risk of HIV Infection* (2005), <http://www.clinicaltrials.gov/ct/show/NCT00002441?order=1>.

²⁵ See CHRIS BEYRER, INTERNATIONAL AIDS VACCINE INITIATIVE, *Injecting Drug Users and HIV Vaccine Trials: What Does the Science Say?*, 6 IAVI REPORT 3, (2002), <http://www.iavireport.org/Issues/0602/idus.asp>; see also Thomas H. Maugh II, *U.S.-Thai Trial for AIDS Vaccine Slated; Medicine: The Joint \$36-million Effort Will Be the Largest Yet*, LOS ANGELES TIMES, July 9, 2002, at 6 (“Critics had argued that it would not be possible to complete the study because of the difficulties involved in monitoring large numbers of high-risk patients for three years or longer”).

²⁶ See CLINICALTRIALS.GOV, NATIONAL INSTITUTES OF HEALTH, *Effectiveness of AIDSVAX B/E Vaccine in Intravenous Drug Users in Bangkok, Thailand* (2005), <http://www.clinicaltrials.gov/ct/show/NCT00006327?order=5>; see also AIDSINFO Phase III, *supra* note 16 (All injection drug users who participated in the trial were automatically enrolled in drug treatment and maintenance programs at the Thai clinics to help them stop using drugs and reduce their risk of HIV infection). According to available estimates, there are anywhere from 100,000 to 250,000 injection drug users in Thailand. HUMAN RIGHTS WATCH, *Thailand, Not Enough Graves: The War on Drugs, HIV/AIDS, and Violations of Human Rights* 2 (June 2004), available at <http://www.hrw.org/reports/2004/thailand0704/thailand0704.pdf> [hereinafter HUMAN RIGHTS WATCH].

²⁷ See AIDS VACCINE CLEARINGHOUSE, AIDS Vaccine Advocacy Coalition, *Frequently Asked Questions: When Will the Next Phase III Trial of an AIDS Vaccine Begin and When Will the Results be Known?*, (2003), at <http://www.aidsvaccineclearinghouse.org/cfaq5.htm>; see also Jane E. Allen, *After a Promising Vaccine Fails in Trials, Researchers Channel Efforts and Optimism Toward Other Possibilities*, LOS ANGELES TIMES, Mar. 3, 2003, Part 6, at 3.

some of the participants are exposed to the HIV virus.²⁸ A document from the U.S. Department of Health and Human Services notes that “[r]egardless of the best efforts at HIV prevention counseling, some individuals will continue to take risks. By comparing the rates of infection among those at risk in both [experimental and control] groups, researchers will be able to determine if the vaccine helps protect these [exposed] individuals from infection.”²⁹ Thus, while the investigators have an ethical obligation to inform participants about minimizing their exposure to HIV, they have a scientific interest in studying individuals who are exposed to the virus.

B. Privately-Funded International Research Creates the Potential for Exploitation of Resource-Deprived Countries

Clinical research has changed significantly in recent years due to increased commercialization of research, proliferation of multi-site trials around the globe,³⁰ and expansion of research into novel areas such as preventive HIV vaccines. VaxGen’s decision to conduct the AIDSVAX clinical trials in the United States and Thailand reflects the growing trend in international biomedical research.³¹ In addition to the increasingly international scope of clinical research, the source of funding has shifted from the public sector to the private sector.³² Although there are many reasons for the expansion of private sector research into developing countries, scientific and financial advantages are probably the most important for pharmaceutical companies.³³ Research subjects in developing countries are generally exposed to fewer drugs than patients in more industrialized countries.³⁴ Conducting trials in developing countries allows pharmaceutical companies to bring their drugs to market faster (due to reduced research costs, access to greater numbers of subjects, and weaker regulations), and to develop new markets for approved drugs.³⁵ In addition,

²⁸ See GRADY, *supra* note 11, at 121 (“To run a scientifically useful study, the community must have a high incidence of HIV and of members at risk of acquiring HIV”).

²⁹ *Id.*

³⁰ See Mark R. Yessian, *Reflections from the Office of the Inspector General*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 10 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

³¹ See Alice K. Page, *Ethical Issues in International Biomedical Research: An Overview*, 37 J. Health L. 629, 633 (2004); see also Emanuel, *supra* note 3, at 289 (“Sponsorship of research is increasingly commercial, and studies are frequently conducted in sites outside the United States”).

³² See Page, *supra* note 31.

³³ *Id.*

³⁴ See RUTH MACKLIN, *DOUBLE STANDARDS IN MEDICAL RESEARCH IN DEVELOPING COUNTRIES* 7 (2004).

³⁵ See Page, *supra* note 31, at 632-33; see also MACKLIN, *supra* note 34, at 7.

financial and regulatory burdens create disincentives for conducting research in countries such as the United States.³⁶

The increasingly private nature of biomedical research raises legal and ethical concerns about the potential for exploitation³⁷ of resource deprived countries.³⁸ Developing countries may not have legal requirements in place for reviewing and conducting research, and may lack the financial resources to implement programs for legal and ethical review of research.³⁹ Thailand has been referred to as both a developing nation and a “newly industrialized” nation, as a reflection of its status between the richest and poorest countries.⁴⁰ Legislation is an important source of law in Thailand,⁴¹ but the legislature has not formally enacted regulatory protections for human subjects.⁴² In response to the increasing presence of HIV in Thailand, public health officials developed a series of “National Plans” to address the problem.⁴³ The National Plans allow Thai officials to coordinate efforts among government agencies to find an effective vaccine and to slow the spread of the HIV epidemic.⁴⁴

However, the fact remains that Thailand lacks formal legislation on human experimentation.⁴⁵ Successive governments have failed to introduce the legislation needed to protect trial subjects, rationalizing that more serious

³⁶ In many cases, multi-center trials are not subject to a single formal oversight structure in the United States. See INSTITUTE OF MEDICINE, RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS 35 (2003).

³⁷ Ruth Macklin, a prominent bioethicist, asserts that “[e]xploitation occurs when wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness, or dependency of others by using the latter to serve their own ends (those of the wealthy or powerful) without adequate compensating benefits for the less powerful or disadvantaged individuals or groups.” MACKLIN, *supra* note 34, at 101-02.

³⁸ See A.A. Hyder et al., *Ethical Review of Health Research: A Perspective From Developing Country Researchers*, 30 J. Med. Ethics 68 (2004).

³⁹ See William Dubois, *New Drug Research, the Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT'L L. 161, 194-96 (2003); see also Page, *supra* note 31, at 633.

⁴⁰ See MACKLIN, *supra* note 34, at 10.

⁴¹ LEGAL SYSTEMS OF THE WORLD: A POLITICAL, SOCIAL, AND CULTURAL ENCYCLOPEDIA, Vol. IV, at 1616 (Herbert M. Kritzer, ed., 2002). Legislative power is vested in the National Assembly (Rathasapha), which is comprised of the Senate (Wuthisapha) and the House of Representatives (Sapha Phuthaen Ratsadon). *Id.*

⁴² See *A Poison Pill?*, BANGKOK POST, Nov. 21, 2001.

⁴³ After the *National AIDS Prevention and Control Plan* (1992-1996), Thailand's National AIDS Prevention and Control Commission formulated the *National Plan for Prevention and Alleviation of HIV/AIDS* (1997-2001), and launched a third *National Plan* for 2002-2006. See AIDSINFO Phase III, *supra* note 16; see also AVERT.ORG, *HIV & AIDS in Thailand* (2005), <http://www.avert.org/aidsthai.htm>.

⁴⁴ See AIDSINFO Phase III, *supra* note 16; see also JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS IN THAILAND, (Draft) *2004 Thailand Country Profile: HIV/AIDS Situation in Thailand and National Response to the Epidemic* (2004), available at http://www.un.or.th/unaidsth/related_document1.php (follow “2004 Thailand Country Profile” hyperlink).

⁴⁵ See *A Poison Pill?*, *supra* note 42.

national problems must be given priority.⁴⁶ Suntaree Vitayanatpaisan, assistant professor of Chulalongkorn's Faculty of Pharmaceutical Sciences, remarked that "[w]e've pushed and pushed to try to finalise legislation to protect trial subjects Is the government trying to say that researchers are allowed to treat humans like guinea pigs?"⁴⁷ Suntaree blames the government bureaucracy for sidelining legislation designed to protect human subjects in Thailand.⁴⁸

In the absence of formal legal protections for human subjects, several university-based ethics committees have been established to monitor biomedical research in Thailand.⁴⁹ The VaxGen trial received an ethics review and approval from the Bangkok Metropolitan Administration, the Faculty of Tropical Medicine of Mahidol University, the Ethical and Scientific Review Committees of the Thailand Ministry of Public Health ("MOPH"),⁵⁰ and the Thailand Food and Drug Administration.⁵¹ In addition, the Thai Safety and Monitoring Board evaluated the results of the trial after thirty months.⁵² While efforts to conduct ethical review in Thailand are commendable, Thailand lacks a formal regulatory body with the "teeth" to enforce such requirements.⁵³ Although the Medical Council of Thailand encourages biomedical researchers to obtain informed consent from trial subjects, without formal legislation, the vulnerable public must rely on researchers' voluntary compliance with ethical standards.⁵⁴

When research is proposed, authorities such as the Thai MOPH may not be in the optimal position to determine what is best for Thai research subjects.⁵⁵ Local researchers stand to gain experience and prestige through international collaboration, and money flows from the researchers to

⁴⁶ Draft legislation to protect human subjects was taken to the National Research Committee in 1975, and then rejected by the Office of the Permanent Secretary for University Affairs; in 1993 a final draft of the legislation was proposed to parliament, but no action was taken. *See id.*

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *See* Aphaluck Bhatiasevi, *AIDS Vaccine Approved by Ethics Panel: Drug Injectors to Take Part in Trial*, BANGKOK POST, Nov. 26, 1997, at 4.

⁵¹ *See* AIDSINFO Phase III, *supra* note 16.

⁵² *See* AIDS/Vaccine Trial: Recruitment of Volunteers 40% Short: Researchers Hopeful of Reaching Target, BANGKOK POST, Mar. 23, 2000.

⁵³ The Forum for Ethical Review Committee in Thailand ("FERCIT") works solely on a voluntary basis; the Medical Council of Thailand steps in only when a subject files a complaint, and does not take a proactive role. *See* *A Poison Pill?*, *supra* note 42.

⁵⁴ *Id.* ("Many researchers don't look for approval from FERCIT or anywhere").

⁵⁵ *See* MACKLIN, *supra* note 34, at 23.

research institutions,⁵⁶ possibly even to the government itself.⁵⁷ In addition, “biomedical research in Thailand could strengthen the nation’s bargaining power with pharmaceutical companies,” when it comes to obtaining essential drugs.⁵⁸

Thai activists note that without legislation to protect research participants, volunteers and communities are open to being exploited by pharmaceutical manufacturers.⁵⁹ Professor Thada Seublinwong of Chulalongkorn University encourages researchers to be “sensitive to community issues as well as individual rights.”⁶⁰ Professor Seublinwong offered the example of researchers using Thai medical facilities and research subjects, and then pulling out all of the resources after the study, which he says would be “unacceptable and unethical.”⁶¹ In fact, the economic motive for the AIDS VAX research was highlighted when VaxGen considered prematurely halting the Thai trials on commercial grounds.⁶² Clinical trials are expensive, and when it became clear that the AIDS VAX vaccine was not effective, VaxGen considered pulling out of Thailand before the final analysis of the data was complete.⁶³ Mahidol University epidemiologist Dwip Kitayaporn noted that VaxGen’s threat of withdrawal from the trial “should teach Thailand and other developing countries to be more careful and not fall into the trap of private business.”⁶⁴

In contrast to the substantial number of financial interests served by clinical research, the Thai MOPH also has a duty to protect the small population of potential research subjects. Wealthy and powerful sponsors such as VaxGen may influence institutions such as the Thai MOPH to approve clinical trials at the expense of the research population.⁶⁵ In their eagerness for an HIV vaccine and research funding, the public health officials and scientists of Thailand failed to protect a small, vulnerable segment of society: the injection drug users who participated in the research. As evidenced by the unscientific desire of VaxGen to halt the

⁵⁶ According to the Drug Issue Research Group, a voluntary group of medical people and activists in Thailand, enormous sums are spent on medical research projects in Thailand every year; a single project can cost up to \$500 million. See *A Poison Pill?*, *supra* note 42.

⁵⁷ See MACKLIN, *supra* note 34, at 23.

⁵⁸ *A Poison Pill?*, *supra* note 42.

⁵⁹ See *id.*

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² See *VaxGen Set to Pull Plug on AIDS Vaccine Trial*, THE NATION (Thailand), July 2, 2003 (“If they leave and allowed all Thai efforts to count for nothing, it could wreck the chances of future clinical trials in developing countries”).

⁶³ See *id.*

⁶⁴ Aphaluck Bhatiasavi, *Ministry Says Vaccine Trial Will Go Ahead*, BANGKOK POST, July 3, 2003.

⁶⁵ See MACKLIN, *supra* note 34, at 23-24; see also *A Poison Pill?*, *supra* note 42.

clinical trial before its completion, the power of profit motive necessitates strong ethical and legal protections. While Thailand has yet to see court battles over human clinical trials, circumstances will likely change if the government fails to take decisive legislative action in the near future.⁶⁶

III. FEDERAL REGULATIONS AND ETHICAL PRINCIPLES ABSENT IN THAILAND PROTECT HUMAN SUBJECTS IN THE UNITED STATES

In recent history, a number of protections have evolved to minimize the harm to research participants. The risk of harm to participants arises because unlike treating physicians, who aim to improve the health of the individual, biomedical researchers seek to advance generalized knowledge that will benefit broader populations, often at the expense of the individual.⁶⁷ In other words, the researcher “must often subordinate an enrollee’s personal interests and desires to the protocol.”⁶⁸ The creation of international guidance documents and domestic laws marked the recognition of the need to protect individual rights over the interest of the researcher in the scientific endeavor.⁶⁹ The principles from international guidance documents are important because they are often used as a definitive source of authority by non-governmental organizations, investigators, and both national and local committees that review the ethical dimensions of research.⁷⁰

A. *Historical Foundations for the Protection of Human Subjects*

Historically, informed consent has functioned as one of the primary protections for human subjects of biomedical research. Informed consent provides a process for ensuring and documenting that a research participant (or his or her legally authorized representative) has acted according to his or her informed, considered, and freely made judgment.⁷¹ Following World War II and Nazi medical experimentation, the Nuremberg Code declared in 1947 that “[t]he voluntary consent of the human subject is absolutely

⁶⁶ See *A Poison Pill?*, *supra* note 42.

⁶⁷ See E. Haavi Morriem, *Litigation in Clinical Research: Malpractice Doctrines Versus Research Realities*, 32 J. L. MED. & ETH. 474, 475 (2004).

⁶⁸ *Id.*

⁶⁹ See Joanne Roman, *U.S. Medical Research in the Developing World: Ignoring Nuremberg*, 11 CORNELL J.L. & PUB. POL’Y 441, 448 (2002).

⁷⁰ See MACKLIN, *supra* note 34, at 19.

⁷¹ See generally Belmont Report, *supra* note 4, at 23,195 (discussing the application of informed consent principles, including the provisions for sufficient information, adequate comprehension, and voluntariness); see also INSTITUTE OF MEDICINE, *supra* note 36, at 95 (noting that obtaining written “informed consent” is tangential to the *process* of informed consent).

essential.”⁷² The Nuremberg Code not only requires the consent of research subjects, but also maintains that the consent must be voluntary (free from coercion), competent, and informed.⁷³

For many years after the creation of the Nuremberg Code, most physicians believed that the Code primarily applied to war crimes, and not to the medical establishment.⁷⁴ Subsequent documents developed by international organizations provided guidelines for ethics in research, and were intended to apply to multinational and intranational research. For example, the Declaration of Helsinki was developed and adopted by the World Medical Assembly in 1964.⁷⁵ In addition to requiring informed consent, the Declaration of Helsinki calls for additional protections for vulnerable and incompetent subjects.⁷⁶ The Declaration of Helsinki also espouses the use of ethical review committees, which are empowered to evaluate “information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects,” and have the right to monitor ongoing trials.⁷⁷

In addition, the World Health Organization (“WHO”) and the Council for International Organizations of Medical Sciences (“CIOMS”) issued a new set of guidelines designed to aid in the application of the Declaration of Helsinki IV.⁷⁸ The 1993 version of the CIOMS guidelines specifically addresses developing countries hosting clinical trials.⁷⁹ In addition to informed consent, the CIOMS guidelines also require that research protocols are prospectively reviewed by independent ethical review bodies.⁸⁰ Guideline 3 specifies that an external sponsoring organization (such as

⁷² See The Nuremberg Code (1947), reprinted in SOURCE BOOK IN BIOETHICS 11-12 (Albert R. Jonsen et al. eds., 1998) [hereinafter Nuremberg Code].

⁷³ See GEORGE J. ANNAS ET AL., INFORMED CONSENT TO HUMAN EXPERIMENTATION 7 (1977).

⁷⁴ See Roman, *supra* note 69, at 451 (noting that the “[b]ecause judges created the Code, and not other researchers, physician-researchers thought the Code inapplicable to their own practices”).

⁷⁵ See WORLD MEDICAL ASSOCIATION, *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (1964), <http://www.wma.net/e/policy/pdf/17c.pdf> (amended in 2000 and clarified in 2002 and 2004) [hereinafter *Declaration of Helsinki*]; see also Roman, *supra* note 69, at 451-52.

⁷⁶ See *Declaration of Helsinki*, *supra* note 75, at paras. 22-24.

⁷⁷ *Id.* at para. 13.

⁷⁸ See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (“CIOMS”) in collaboration with the WORLD HEALTH ORGANIZATION (“WHO”), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), http://www.cioms.ch/frame_guidelines_nov_2002.htm [hereinafter *CIOMS Guidelines*]; see also LAWRENCE O. GOSTIN & ZITA LAZZARINI, HUMAN RIGHTS AND PUBLIC HEALTH IN THE AIDS PANDEMIC 128 (1997).

⁷⁹ The CIOMS Guidelines require investigators to obtain voluntary informed consent from every prospective subject, but they also recognize that it may be challenging to obtain informed consent from subjects in countries with low levels of education. See *CIOMS Guidelines*, *supra* note 78, at Guideline 4.

⁸⁰ See *CIOMS Guidelines*, *supra* note 78, at Guideline 2.

VaxGen) should submit the research protocol for ethical and scientific review “in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country.”⁸¹

The Joint United Nations Programme on HIV/AIDS (“UNAIDS”) has also issued a guidance document titled “Ethical Considerations in HIV Preventive Vaccine Research,” which directly relates to the VaxGen clinical trials in Thailand.⁸² The UNAIDS document highlights some of the special issues that ethical review committees should consider when reviewing international research. First, HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review.⁸³ Additionally, the research protocol should describe the social contexts of a proposed research population, so that reviewing bodies can evaluate whether there may be exploitive conditions or increased vulnerability among potential research participants.⁸⁴ Like other guidance documents, UNAIDS requires informed consent, as well as a plan for monitoring the continuing adequacy of consent among research subjects.⁸⁵ In addition, UNAIDS specifically calls for special measures to protect persons, including intravenous drug users, who may be limited in their ability to give informed consent due to their social or legal status.⁸⁶

While the aforementioned documents declare the importance of informed consent and suggest the utility of prior independent ethical review to protect human subjects, none create legally enforceable obligations for states or individuals.⁸⁷ Nonetheless, the Nuremberg Code and Declaration of Helsinki,⁸⁸ and to a lesser extent, the CIOMS and UNAIDS guidelines, have all influenced the creation of law and policy in the United States. Accordingly, U.S. regulations incorporate the legal and ethical requirements of informed consent and prior ethical review.

⁸¹ *Id.* at Guideline 3.

⁸² See JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS), UNAIDS Guidance Document, *Ethical Considerations in HIV Preventive Vaccine Research* (2000), http://www.unaids.org/html/pub/publications/irc-pub01/jc072-ethicalcons_en_pdf.pdf [hereinafter UNAIDS Guidance].

⁸³ *Id.* at 21.

⁸⁴ *Id.* at 22.

⁸⁵ *Id.* at 32, 39.

⁸⁶ *Id.* at 36-37.

⁸⁷ See Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT’L L. 513, 531 (2002); see also Finnuala Kelleher, *The Pharmaceutical Industry’s Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J. L. & SOC. PROBS. 67, 80-81 (2004).

⁸⁸ The U.S. federal regulations of human subjects research specifically reference both the Nuremberg Code and the Declaration of Helsinki. See Chang, *supra* note 2, at 346.

B. *The Belmont Report Provides the Ethical Foundations for the Protection of Human Subjects in the United States*

In the United States, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research created the Belmont Report to provide an “analytical framework” for the resolution of “ethical problems arising from research involving human subjects.”⁸⁹ The Belmont Report identified three ethical principles that govern research on human subjects: (1) respect for persons (autonomy), (2) beneficence, and (3) justice.⁹⁰

The principle of respect for persons is comprised of two moral requirements: (1) that individuals should be treated as autonomous agents, and (2) that persons with diminished autonomy are entitled to protection.⁹¹ The Belmont Report clarifies those requirements, explaining that for most research on human subjects “respect for persons demands that subjects enter into the research voluntarily and with adequate information.”⁹² In other words, the principle of respect for persons requires the provision of informed consent. Informed consent is assessed according to the adequacy of the information, comprehension by the subject, and voluntariness (consent free of coercion and undue influence).⁹³

According to the Belmont Report, the principle of “beneficence” can be expressed by two general rules: “(1) do not harm, and (2) maximize possible benefits and minimize possible harms.”⁹⁴ While a research subject can balance the risks and benefits of participation individually, ethical review committees must also weigh these factors on behalf of the study population.

The principle of “justice” requires a fair distribution of the risks and benefits in the selection of research subjects.⁹⁵ Justice is a particularly important factor to consider in the context of international research, because it implies that certain nations and populations must not disproportionately bear the burdens of biomedical research.⁹⁶ Justice concerns have often focused on the exploitation of subjects in developing countries with regard

⁸⁹ See Belmont Report, *supra* note 4, at 23,193.

⁹⁰ *Id.* at 23,193-94.

⁹¹ *Id.* at 23,193.

⁹² *Id.* at 23,194.

⁹³ *Id.* at 23,195.

⁹⁴ *Id.* at 23,194.

⁹⁵ *Id.*

⁹⁶ See *id.* at 23,196 (“Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only ‘undesirable’ persons for risky research”).

to subject recruitment.⁹⁷ The Belmont Report cautions that vulnerable populations should be “protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.”⁹⁸ Justice demands that the risks and benefits of research are spread evenly across the globe, and that cost-benefit ratios do not vary with geographic location.⁹⁹ By promoting the concepts of respect for persons, beneficence, and justice, the Belmont Report provides the ethical foundation for the current federal laws governing research on human subjects in the United States.

C. *The Statutory Basis for Protecting Human Subjects Derives from the Common Rule and FDA Regulations*

Federal regulations implement the ethical principles of the Belmont Report,¹⁰⁰ but the regulations only control certain types of research on human subjects. Two separate sections of the Code of Federal Regulations may apply to clinical trials on human subjects, depending on the funding source.

The Common Rule was created in 1991 when the President’s Commission recommended that all federal agencies adopt U.S. Department of Health and Human Services (“DHHS”) regulation 45 CFR part 46, governing research on human subjects.¹⁰¹ Subpart A of the regulations was thereafter endorsed by seventeen federal agencies and departments that fund research on human subjects,¹⁰² creating a unified system of protections. If a clinical trial involving human subjects is conducted by the federal government, supported by federal grants, or otherwise subject to regulation by a federal department or agency, the Common Rule applies.¹⁰³

Under certain circumstances, compliance with the Common Rule may not be legally required of a clinical trial involving human subjects.¹⁰⁴ For

⁹⁷ See MACKLIN, *supra* note 34, at 68.

⁹⁸ See Belmont Report, *supra* note 4, at 23,197.

⁹⁹ See Ruth Macklin, *Justice in International Research*, in BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 132 (Jeffrey P. Kahn et al. eds., 1998).

¹⁰⁰ See Berman, *supra* note 10, at 308.

¹⁰¹ See GRADY, *supra* note 12, at 44-45 (The DHHS regulations were originally codified in 1981 at 45 C.F.R. § 46, and were most recently revised in 1991); see also Sharona Hoffman, *Regulating Clinical Research: Informed Consent, Privacy, and IRBs*, 31 CAP. U. L. REV. 71, 75 (2003).

¹⁰² See INSTITUTE OF MEDICINE, *supra* note 36, at 138; see also Emanuel, *supra* note 3, at 282.

¹⁰³ 45 C.F.R. §§ 46.101(a), 46.102(e) (2005). U.S. federal policy requires that each institution engaged in federally sponsored human subject research file an “assurance” of compliance with the Office of Human Research Protections (“OHRP”). See Laura A. McNay et al., *Regulatory Approvals in a Large Multinational Clinical Trial: the ESPRIT Experience*, 23 CONTROLLED CLINICAL TRIALS 59, 60-61 (2002).

¹⁰⁴ See Emanuel, *supra* note 3, at 283.

example, research that is entirely funded by private sources (rather than government sources) lacks the requisite federal nexus for the Common Rule to apply.¹⁰⁵ In the case of privately-funded research by pharmaceutical companies, the federal government would need an additional basis for regulating.

The FDA did not sign on to the Common Rule, and therefore has a separate basis for regulating research on human subjects.¹⁰⁶ The FDA applies requirements similar to the Common Rule to clinical research conducted as a part of the approval process for drugs, devices, or biologics (which include vaccines).¹⁰⁷ When a sponsor of a drug or vaccine seeks to study the product to learn if it is suitable for marketing, the sponsor must file an investigational new drug application (“IND”) with the FDA.¹⁰⁸ If IND approval is secured by an investigator, then the study may begin, subject to strict compliance with the protocols accepted by the FDA.¹⁰⁹ Even if a private pharmaceutical company conducts research on populations outside of the United States,¹¹⁰ the research will be subject to FDA requirements if the company ultimately intends to seek FDA approval for use of the product in the United States.¹¹¹ FDA regulations unquestionably have full legal effect in the United States, and compliance is mandatory.¹¹²

In sum, the federal system of protections applies only to research funded by a federal agency that is subject to the Common Rule, and to private entities that will ultimately seek FDA review and approval.¹¹³

¹⁰⁵ 45 C.F.R. § 46.101(a).

¹⁰⁶ See Emanuel, *supra* note 3, at 282 (discussing 21 C.F.R. §§ 50, 56 (2005)); see also Chang, *supra* note 2, at 341-42.

¹⁰⁷ See Emanuel, *supra* note 3, at 282.

¹⁰⁸ See Dale E. Hammerschmidt, *Understanding the FDA's IND Process*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 323 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002). The overarching purposes of the IND process are to “ensure the rights and welfare of study subjects and to ensure the quality and integrity of the data on which licensing applications are based.” *Id.* at 325.

¹⁰⁹ *Id.* at 325.

¹¹⁰ 45 C.F.R. § 46.101(a); 21 C.F.R. § 50.1(a).

¹¹¹ 45 C.F.R. § 46.102(e).

¹¹² FDA's Center for Biologics Evaluation and Research (“CBER”) is responsible for regulating vaccines in the United States. See David G. Forster & Gary L. Chadwick, *International Conference on Harmonisation*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 316 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002); see also U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Vaccine Product Approval Process*, July 27, 2002, available at <http://www.fda.gov/cber/vaccine/vacappr.htm> (current authority for the regulation of vaccines resides primarily in Section 351 of the Public Health Service Act and specific sections of the Federal Food, Drug and Cosmetic Act).

¹¹³ See INSTITUTE OF MEDICINE, *supra* note 36, at 138.

D. *The Federal Regulations Create Safeguards for Research Subjects*

The Common Rule and the FDA regulations, as well as the aforementioned international declarations and guidelines, require two primary protections for research subjects: individual voluntary informed consent, and prior review of proposed research by an independent ethical review committee.¹¹⁴ Ethical evaluation of clinical trials using the Belmont Report framework is often required to ensure that the regulations are appropriately implemented.

I. *Individual Voluntary Informed Consent Promotes Autonomy and Beneficence*

The general requirements for informed consent are virtually identical in the Common Rule and the FDA regulations.¹¹⁵ Subjects (or their legally authorized representatives) must give “legally effective informed consent” in order to participate in research.¹¹⁶ To clarify the information that must be provided to a research subject (or their legally authorized representative), the regulations list eight basic elements:

(1) a statement that the study involves research, as well as a description of the research and its purposes; (2) a description of reasonably foreseeable risks; (3) a description of reasonably expected benefits; (4) disclosure of appropriate alternatives; (5) a statement about maintenance of confidentiality; (6) for research involving more than minimal risks, an explanation about possible compensation if injury occurs; (7) information about how the subject can have pertinent questions answered; and (8) a statement that participation is voluntary (i.e., refusal to participate involves no penalties or loss of benefits).¹¹⁷

It is important for investigators to understand the difference between “the presentation of the information, and even the signing of the consent document, and bona fide consent.”¹¹⁸ A document with a signature is not consent, but is merely a record of what was supposed to have been

¹¹⁴ Emanuel, *supra* note 3, at 282.

¹¹⁵ See 45 C.F.R. 46 § 116 (2005); 21 C.F.R. § 50.20 (2005); see also Bonnie M. Lee, U.S. FOOD AND DRUG ADMINISTRATION, *Comparison of FDA and HHS Human Subject Protection Regulations*, 2000, available at <http://www.fda.gov/oc/gcp/comparison.html>.

¹¹⁶ See 45 C.F.R. § 46.116 (2005).

¹¹⁷ *Id.* at § 46.116; 21 C.F.R. § 50.25 (2005).

¹¹⁸ Robin L. Penslar, *The IRB's Role in Editing the Consent Document*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 233 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

communicated between researchers and prospective participants.¹¹⁹ According to the Belmont Report, informed consent is evaluated by the adequacy of the information provided, the subject's comprehension of the information, and the voluntariness of the consent.¹²⁰

2. *Prior Independent Ethical Review Strengthens Informed Consent and Promotes Beneficence and Justice*

Institutional Review Boards ("IRBs") are responsible for reviewing the ethical facets of proposed human research. When research is not subject to federal regulation, investigators "are under no formal obligation to monitor the ethical aspects of research," but may voluntarily elect to do so.¹²¹ In contrast, all clinical trials under federal jurisdiction must be examined and approved by a U.S. IRB prior to commencement.¹²² IRBs are required by the federal regulations to ensure that: (1) informed consent is obtained from subjects and documented (respect for persons, or autonomy),¹²³ (2) the risks to subjects are minimized and are reasonable in relation to benefits (beneficence),¹²⁴ and (3) the selection of subjects is equitable (justice).¹²⁵

Privately-funded researchers that are not required to comply with the Common Rule must comply with FDA regulations¹²⁶ when research involves the investigational use of biologics such as vaccines, and the institution plans to market the biologic in the United States, regardless of the source of funding.¹²⁷ However, if an institution conducts research that is subject to both the Common Rule and the FDA regulations, the IRB review must comply with both sets of regulations.¹²⁸ Requiring researchers and review

¹¹⁹ See INSTITUTE OF MEDICINE, *supra* note 36, at 95; see also Office for the Protection From Research Risks (now Office for Human Research Protections), U.S. Department of Health and Human Services, *Tips on Informed Consent* (1993), <http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm>.

¹²⁰ See Belmont Report, *supra* note 4, at 23,195.

¹²¹ Robert J. Amdur & Elizabeth A. Bankert, *The IRB: Definition and Federal Oversight*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 27 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

¹²² In the U.S., research on human subjects must be approved by the appropriate IRB. 45 C.F.R. § 46.101(a)(2) (2005); see generally Barbara A. Noah, *Bioethical Malpractice: Risk and Responsibility in Human Research*, 7 J. HEALTH CARE L. & POL'Y 175, 181-206 (2004); Hoffman, *supra* note 101, at 76; Berman, *supra* note 10, at 309; Chang, *supra* note 88, at 342.

¹²³ 45 C.F.R. § 46.111(a)(4), 46.111(a)(5) (2005); 21 C.F.R. §§ 56.111(a)(4), 56.111(a)(5) (2005).

¹²⁴ 45 C.F.R. §§ 46.111(a)(1), 46.111(a)(2) (2005); 21 C.F.R. §§ 56.111(a)(1), 56.111(a)(2) (2005).

¹²⁵ 45 C.F.R. § 46.111(a)(3) (2005); 21 C.F.R. § 56.111(a)(3) (2005).

¹²⁶ 21 C.F.R. §§ 56.103 (2005).

¹²⁷ See Robert J. Amdur, *Differences Between DHHS and FDA Regulations*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 329 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

¹²⁸ *Id.*

committees to implement informed consent and ethical principles helps to ensure the equitable selection of subjects from diverse populations.¹²⁹

D. United States Regulations Apply to U.S.-Based Research Conducted in Thailand

Informed consent and IRB review protect the rights and welfare of research subjects in the United States by promoting autonomy, beneficence, and justice. The strength of the protections must not be compromised when U.S. pharmaceutical companies conduct research abroad, particularly where clinical trials are conducted in vulnerable populations.¹³⁰ In addition to Thai protections, United States federal regulations represent another layer of protection for research subjects.

In the case of the AIDSVAX clinical trials, determining whether the Common Rule applies to research conducted outside U.S. borders is not a straightforward task. If international research is funded through the Department of Health and Human Services (“DHHS”), then the Common Rule unquestionably applies. However, the AIDSVAX trial was funded by VaxGen, a private pharmaceutical company that developed the AIDSVAX vaccine. Despite the private nature of the funding, collaboration between the U.S. federal government and researchers in Thailand created a sufficient federal nexus to bring the research within the reach of the Common Rule.

The National Institutes of Health (“NIH”) issued guidelines to help investigators determine whether collaborative research between intramural investigators and others in the United States and abroad is covered by federal requirements.¹³¹ According to the NIH, collaborative activities may include “substantive intellectual contributions to research techniques, protocol design, or interpretation of data.”¹³² If VaxGen collaborated with an entity supported by the NIH or another DHHS entity, then the research would be subject to the Common Rule. The NIH declined to provide direct funding for the AIDSVAX trials, but the Centers for Disease Control and Prevention (“CDC”) collaborated with both United States and Thai institutions by providing epidemiologic and laboratory technical

¹²⁹ See 45 C.F.R. §§ 46.111(a)(3), 46.111(a)(4).

¹³⁰ See CIOMS Guidelines, *supra* note 78, at Guideline 13.

¹³¹ See NATIONAL INSTITUTES OF HEALTH, *Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health*, 12 (2004), available at <http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf>.

¹³² *Id.*

assistance.¹³³ The CDC assisted researchers in Thailand with statistical analysis (interpreted results, determined whether the vaccine was effective), consulted on implementation strategies and access, and conducted studies on the subject population.¹³⁴ The CDC arguably “collaborated” with VaxGen when it provided “substantive intellectual contributions,” thus bringing the AIDSVAX research within the purview of the Common Rule.¹³⁵

Additionally, the United States exercises control over the introduction of new pharmaceutical products into the U.S. marketplace through the FDA, which requires informed consent¹³⁶ and IRB review¹³⁷ for research on human subjects. Institutions that are not required to follow the Common Rule must comply with the FDA regulations when research involves the investigational use of biologics (such as vaccines), regardless of the source of research funding.¹³⁸ Since the VaxGen vaccine products would ultimately require FDA approval, the research is subject to federal regulation by virtue of the FDA statute.¹³⁹

IV. UNITED STATES PROTECTIONS FOR HUMAN SUBJECTS WERE IMPROPERLY APPLIED TO THE THAI VACCINE TRIALS

United States research regulations and practices cannot be directly applied in Thailand, where many cultural, social, and political factors operate to undermine the effectiveness of the protections. In assessing whether the legal requirements for informed consent and IRB review are met, research should be measured against the underlying ethical principles that gave rise to the U.S. laws.¹⁴⁰ The ethical substance of the U.S. regulations must be maintained in Thailand, even amid vastly different circumstances, because different contexts do not allow for the use of a lower ethical standard in assessing legal compliance.¹⁴¹ Researchers and review

¹³³ See UNAIDS VACCINE ADVISORY COMMITTEE, *Report from the Meeting of the UNAIDS Vaccine Advisory Committee*, Geneva, 10 (1999), available at http://www.who.int/vaccine_research/diseases/hiv/policy/en/report_june_99.pdf; see also AIDSINFO Phase III, *supra* note 16.

¹³⁴ See CENTERS FOR DISEASE CONTROL AND PREVENTION, *NCHSTP Program Briefing 2001: HIV Vaccine Research* (2001), http://www.cdc.gov/nchstp/od/program_brief_2001/HIV%20Vaccine%20Research.htm.

¹³⁵ See NATIONAL INSTITUTES OF HEALTH, *supra* note 131.

¹³⁶ 21 C.F.R. § 50.20.

¹³⁷ 21 C.F.R. § 56.103.

¹³⁸ See Amdur, *supra* note 127, at 329.

¹³⁹ *Id.*; 21 C.F.R. § 56.103.

¹⁴⁰ See Gerald S. Schatz, *Are the Rationale and Regulatory System for Protecting Human Subjects of Biomedical and Behavioral Research Obsolete and Unworkable, or Ethically Important but Inconvenient and Inadequately Enforced?*, 20 J. CONTEMP. HEALTH L. & POL'Y 1, 31 (2003).

¹⁴¹ See Page, *supra* note 31, at 641-42.

boards must account for the factors in Thai culture that create special harms and vulnerabilities for the research population.

A. *Informed Consent in Thailand was Inadequate*

According to the Belmont Report framework, scientific research on human subjects must adhere to three ethical requirements for informed consent: adequate information, comprehension by the subject, and voluntariness, or the absence of coercion.¹⁴² The informed consent provisions of the Common Rule and the FDA regulations incorporate these ethical components.¹⁴³ As a developing nation, Thailand presents researchers with “unique challenges” during the process of obtaining informed consent.¹⁴⁴ In addition to concepts about research and individual choice that might be unfamiliar, participants “may be plagued by poverty, illiteracy, and limited access to health care services that make it difficult for them to give valid informed consent.”¹⁴⁵ In the case of the AIDSVAX vaccine trials, conditions in Thailand, as well as the decision to study a population of injection drug users, created challenges for the informed consent process that did not exist in the United States.

1. *The Information Provided to Research Subjects was Inappropriate or Inaccurate for the Thai Population of Injection Drug Users*

Researchers in Thailand need to provide meaningful information through culturally appropriate channels, because the information necessary for informed consent involves complex concepts.¹⁴⁶ Researchers should present information that is appropriate for “research subjects from different backgrounds and with varying levels of education” to allow for a clear understanding of the nature and purpose of the research, and to promote “an informed and considered decision” about participation.¹⁴⁷

In vaccine clinical trials, complex scientific concepts such as “placebo” and “randomization” must be explained to potential volunteers. In a placebo-controlled design, some of the participants receive the vaccine

¹⁴² See Belmont Report, *supra* note 4, at 23,195.

¹⁴³ See generally 45 C.F.R. § 46 (2005) and 21 C.F.R. § 56 (2005).

¹⁴⁴ See Page, *supra* note 31, at 648.

¹⁴⁵ Christine Pace et al., *The Quality of Informed Consent in a Clinical Research Study in Thailand*, 27 IRB: ETHICS & HUMAN RESEARCH 9 (2003).

¹⁴⁶ See Baruch A. Brody, *Making Informed Consent Meaningful*, 23 IRB: ETHICS & HUMAN RESEARCH 1, 3 (2001) (“Of particular importance is the development of useful general language that promotes an understanding of the general features of clinical trials”).

¹⁴⁷ Page, *supra* note 31, at 648.

being tested, known as the “experimental group,” and the others receive no vaccine, known as the “placebo group.”¹⁴⁸ The determination of which subjects get the vaccine and which do not is made by a process of “randomization.” For example, of the 2,500 Thai volunteers, half were randomly given the AIDSVAX vaccine and the other half received placebo injections that did not include the vaccine.¹⁴⁹

When conceptually challenging issues such as placebos and randomization must be explained in order for participants to understand the research, particular care should be taken to ensure that explanations are clear and translations are appropriate. In one clinical trial, when the U.S. and Thai consent forms were compared, it was determined that the Thai form was less clear in its definition of a “placebo.”¹⁵⁰ When this difference was brought to the attention of the Thai Ministry of Public Health, rather than clarifying the term, the Director defended the translation as being “appropriate and clear and understandable in its description of the concept of an inactive comparison pill, or placebo.”¹⁵¹ A later study of Thai research participants reinforced the idea that “randomization” was a problematic concept for participants to understand.¹⁵²

Another concept that should be clarified when obtaining informed consent from Thai research participants is the distinction between medical treatment and experimental research. Several cultural reasons make truly informed consent difficult to achieve in Thailand at the present time, including the “relative lack of understanding of the nature of medical research in the lay population.”¹⁵³ The doctor-patient relationship involves treatment for the benefit of the individual, while the researcher-subject relationship is not undertaken for the benefit of the individual participant.¹⁵⁴ Whereas the individual subject is primarily concerned with improving their health, the researcher seeks generally applicable scientific knowledge, which does not necessarily provide any benefit to the subject’s health.¹⁵⁵

¹⁴⁸ See AIDSINFO Phase III, *supra* note 16.

¹⁴⁹ *Id.*

¹⁵⁰ See Abinash Achrekar & Rajesh Gupta, Letter to the Editor, *Informed Consent for a Clinical Trial in Thailand*, 339 NEW ENGLAND J. MED. 1331-1332 (1998).

¹⁵¹ *Id.*

¹⁵² See Pace, *supra* note 145, at 14.

¹⁵³ Panuwat Lertsithichai, *Medical Research Ethics in Thailand: What Should Be the Most Appropriate Approach? An Analysis Based on Western Ethical Principles*, 87 J. MED. ASSOC. THAI. 1253, 1255 (2004).

¹⁵⁴ See JESSICA W. BERG et al., INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE 279-80 (2d ed. 2001); Morreim, *supra* note 67, at 475.

¹⁵⁵ See BERG, *supra* note 154, at 280; see also Morreim, *supra* note 67, at 475.

In addition to providing the appropriate information, the method by which the information is conveyed is also important for informed consent. The traditional one-on-one informed consent process commonly used in Western cultures may not be the best practice in Thailand.¹⁵⁶ Researchers have noted that “[i]n all fields of medicine, not just HIV/AIDS, Thai subjects tend to be dominated by the health professional in the doctor-patient relationship.”¹⁵⁷ For cultural reasons, open group interaction may be more appropriate in Thailand, where potential research participants are allowed to share experiences with peers when making decisions.¹⁵⁸

2. *Researchers Did Not Adequately Address Barriers to the Comprehension of Injection Drug Users*

For informed consent to be truly valid, Thai research subjects must actually comprehend the information they are given. However, a number of barriers to effective comprehension exist in the Thai study population, including illiteracy, injection drug use, misconceptions about the nature of research, and confusing recruitment practices. A 1999 study of the comprehension and motives of volunteers for participating in medical research in Thailand¹⁵⁹ noted that literacy may be a barrier to comprehension for some, particularly for those who lacked a secondary education.¹⁶⁰ When most research participants come from lower-educated segments of the Thai population, the use of technical language in informed consent documents may be inappropriate for the intended audience.¹⁶¹ The previously discussed problems in translating research concepts (such as “placebo”) from English to Thai may exacerbate comprehension problems in subjects with literacy difficulties.

In addition to general concerns about comprehension among Thai research participants, special issues arise due to the characteristics of the research population. The group of subjects recruited for the clinical trials in

¹⁵⁶ See Pace, *supra* note 145, at 10.

¹⁵⁷ *Id.*

¹⁵⁸ See *id.*

¹⁵⁹ See Kathleen M. MacQueen et al., *Willingness of Injection Drug Users to Participate in an HIV Vaccine Efficacy Trial in Bangkok, Thailand*, 21 JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES 243, 244 (1999).

¹⁶⁰ *Id.* at 249.

¹⁶¹ See Hoffman, *supra* note 101, at 83; see also Michael K. Paasche-Orlow et al., *Readability Standards for Informed Consent Forms as Compared with Actual Readability*, 348 N. Engl. J. Med. 721, 722 (2003) (“Institutional review boards are charged with safeguarding potential subjects with limited literacy, but they may have an inadvertent role in promulgating unreadable informed-consent forms”).

Thailand was entirely comprised of injection drug users.¹⁶² Addicts may not be able to give informed consent to treatment,¹⁶³ even assuming that they are not under the influence of drugs at the time of recruitment.¹⁶⁴ It is clear that acutely intoxicated people are impaired in their decisionmaking, but it is “less obvious to what extent these individuals are still decisionally impaired when they are not intoxicated.”¹⁶⁵ When research subjects are selected from a group of injection drug users, it raises questions about the ability of the subjects to comprehend the research to which they are consenting.

Volunteers should not be categorically excluded from clinical trials for merely belonging to the general class of injection drug users. However, researchers must consider whether an actual impairment of decisional capacities would make voluntary research participation problematic for such individuals.¹⁶⁶ A report by the National Bioethics Advisory Committee (“NBAC”) proposed that “subjects failing to exhibit a minimal degree of concern for [their] welfare should be deemed incapable of independent decision making.”¹⁶⁷ Although the Thai study participants were enrolled in drug treatment programs, it is unlikely that all participants had successfully abandoned their addictions at the time of the trial. Former and recovering addicts may be able to give informed consent to research if certain criteria have been met, such as being free from intoxication or withdrawal, as well as not having an intense “craving” at the time informed consent is obtained.¹⁶⁸ In short, the presence of drug addiction at the time of enrollment should trigger a special inquiry about the decisional fitness of the volunteer.

In some circumstances, a basic misunderstanding about the nature of clinical research can undermine the comprehension element of informed consent. The mistaken belief among subjects that the principle of personal

¹⁶² See Suphak Vanichseni et al., *Recruitment, Screening and Characteristics of Injection Drug Users Participating in the AIDSVAX B/E HIV Vaccine Trial*, Bangkok, Thailand, 18 AIDS 311, 312 (2004); see also CLINICALTRIALS.GOV, Effectiveness of AIDSVAX B/E Vaccine in Intravenous Drug Users in Bangkok, Thailand, *supra* note 26.

¹⁶³ See M. Susan Ridgely & Martin Y. Iguchi, *Coercive Use of Vaccines Against Drug Addiction: Is It Permissible and Is It Good Public Policy?*, 12 VA. J. SOC. POL’Y & L. 260, 280 (2004); see also BERG *supra* note 154, at 270.

¹⁶⁴ See Peter J. Cohen, *Untreated Addiction Imposes an Ethical Bar to Recruiting Addicts for Non-therapeutic Studies of Addictive Drugs*, 30 J. L. MED. & ETHICS 73, 73-74 (2002).

¹⁶⁵ *Id.* at 73.

¹⁶⁶ See Gavin W. Hougham et al., *Empirical Research on Informed Consent with the Cognitively Impaired*, 25 IRB: ETHICS & HUMAN RESEARCH 26 (2003).

¹⁶⁷ See NATIONAL BIOETHICS ADVISORY COMMISSION, *Research Involving Subjects with Mental Disorders That May Affect Decisionmaking Capacity* (1998), <http://onlineethics.org/reseth/nbac/mchapter2.html>.

¹⁶⁸ See Cohen, *supra* note 164, at 76.

care applies in the research setting has been termed the “therapeutic misconception.”¹⁶⁹ In research involving healthy volunteers such as the AIDSVAX trials, subjects may assume that physicians will not suggest enrollment unless the vaccine is very likely to be of help to participants, and that the risks of participation are low.¹⁷⁰ For example, the clinical trials of the AIDSVAX vaccine involved the use of placebos, so only half of the volunteers actually received the vaccine. If the vaccine had actually been effective, then half of the participants had no chance of benefiting from the vaccine. In this case, because the vaccine was shown to be ineffective, none of the study participants received any health benefits from the vaccine trials. Therefore, it is important for volunteers to understand that clinical trials do not constitute a form of treatment.

The recruitment practices employed in Thailand were one factor that likely contributed to the therapeutic misconception among Thai participants. Drug treatment differs from medical treatment in certain respects, but the therapeutic misconception may be applicable to the AIDSVAX trial. Injection drug users who enrolled in the AIDSVAX trials were recruited from Bangkok narcotic treatment clinics.¹⁷¹ Recruiting subjects at treatment centers is an attractive option for researchers because it provides access to large numbers of potential subjects at a single site. Clinical research is facilitated when the subject population is convenient, “both in terms of availability for recruitment and for monitoring through the course of the study.”¹⁷² Initially, drug users came to know and trust the staff at Bangkok Metropolitan Administration (BMA) narcotic clinics, where they received individual benefits from the methadone treatment. Then, other researchers visited these injection drug users at BMA facilities to request their participation in a clinical trial. One of the reasons for the willingness of drug users to participate in the trials was likely the “atmosphere of trust between BMA staff and IDU [injection drug users].”¹⁷³ As a result of their trust in the BMA staff, injection drug users may have agreed to participate in clinical research under the mistaken assumption that they would personally benefit from participating.

¹⁶⁹ See Paul S. Appelbaum et al., *The Therapeutic Misconception: Informed Consent in Psychiatric Research*, 5 INT. J.L. PSYCHIATRY 319, 327-28 (1982).

¹⁷⁰ See Paul S. Appelbaum et al., *Therapeutic Misconception in Clinical Research: Frequency and Risk Factors*, 26 IRB: ETHICS & HUMAN RESEARCH 1, 2 (2004).

¹⁷¹ See Vanichseni *supra* note 162, at 312.

¹⁷² Jonathan D. Moreno, *Convenient and Captive Populations*, in BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 111 (Jeffrey P. Kahn, et al. eds., 1998).

¹⁷³ Vanichseni *supra* note 162, at 315.

When subjects fail to appreciate the nature of research, they may fail to comprehend and clearly evaluate the risk/benefit ratio for the project to which they are being asked to consent.¹⁷⁴ When the subject misunderstands the nature of the research, a decision to participate “raises concerns about the autonomy of that decision.”¹⁷⁵ The operation of HIV vaccine clinical trials in Thailand illustrates the concept of therapeutic misconception in practice. The difficulty of obtaining truly informed consent in Thailand is related to the manner in which subjects are recruited, as well as the fact that the subjects are members of a socially vulnerable segment of the Thai population.

3. *Social and Political Factors in Thailand Compromised the Voluntariness Element of Informed Consent*

The Thai clinical trials lacked the element of voluntariness more than any other aspect of informed consent. Collectively, injection drug users are a marginalized, socially vulnerable segment of Thai society.¹⁷⁶ A report from the U.S. National Bioethics Advisory Commission (“NBAC”) on research with human subjects recommended that vulnerability be assessed on the basis of individual characteristics, rather than group membership.¹⁷⁷ The six categories of vulnerability proposed by NBAC included cognitive, institutional, deferential, medical, economic, and social.¹⁷⁸ Injection drug users are often incarcerated or committed to treatment programs, and occupy a relatively low status in society.¹⁷⁹ Given that nearly every category described by NBAC could apply to Thai injection drug users, they constitute a vulnerable population.¹⁸⁰ Despite their vulnerable status, vaccine clinical trials follow injection drug users because they engage in many practices that create high risks for contracting HIV.¹⁸¹

¹⁷⁴ See BERG, *supra* note 154, at 290 (“[P]atients, in their eagerness to become subjects of the study in order to receive the restricted treatment, will fail to attend to other information that might alter their assessment of the value of participation”).

¹⁷⁵ Sam Horng & Christine Grady, *Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism*, 25 IRB: ETHICS & HUMAN RESEARCH 11, 12 (2003).

¹⁷⁶ See *Between the Lines: Ethical Practices Must Be Held Foremost in Drug Trials*, THE NATION (Thailand), Dec. 11, 2004.

¹⁷⁷ See NATIONAL BIOETHICS ADVISORY COMMISSION (“NBAC”), *Ethical and Policy Issues in Research Involving Human Participants*, Vol. I at 87-88 (August 2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf> [hereinafter NBAC].

¹⁷⁸ *Id.* at 88-91.

¹⁷⁹ See Ridgely, *supra* note 163, at 265.

¹⁸⁰ NBAC, *supra* note 177, at 87.

¹⁸¹ See INSTITUTE OF MEDICINE, AIDS AND BEHAVIOR: AN INTEGRATED APPROACH 53-56 (1994).

Negative social attitudes toward injection drug users are evidenced by the lack of political will to curb the spread of HIV infection among Thailand's drug users.¹⁸² In contrast to other at-risk groups, such as sex workers and military recruits, HIV prevalence among Thailand's injection drug users has never dropped.¹⁸³ In fact, drug users are "projected to account for 30 percent of new HIV infections in Thailand by 2005, a higher percentage than any other group."¹⁸⁴ Yet many people with HIV/AIDS who want to recover from drug addictions find it "difficult to get access to treatment because of discrimination in their communities."¹⁸⁵

In addition to the lack of social programs for drug users with HIV/AIDS in Thailand, recent political movements have been characterized by significant violations of the legal rights of injection drug users. Since taking office in 2001, one of Prime Minister Thaksin Shinawatra's top priorities has been the "prevention and suppression" of narcotic drugs, which has negatively impacted drug users.¹⁸⁶ When the government campaign against drug use was officially launched in February 2003, it resulted in approximately 2,275 extrajudicial killings of drug users within the first three months, the "arbitrary arrest or blacklisting of several thousand more...the endorsement of extreme violence by government officials at the highest levels," and coerced or mandatory drug treatment.¹⁸⁷

Thai police typically profile drug users based on factors such as syringe markings on their arms or attendance at methadone clinics. Those who meet the criteria are often arrested and forced to confess to drug-related crimes.¹⁸⁸ These methods of tracking and profiling individuals can have negative implications for the safety of anyone associated with drug use, including participants in HIV vaccine trials carried out exclusively on injection drug users. In an environment where the rights of individuals with substance abuse problems are disregarded, it seems unlikely that their autonomy interests would be afforded much value.

¹⁸² Despite recommendations by WHO favoring syringe exchange programs, and the proven track record of such programs in reducing HIV transmission without increasing drug use, the Thai government is opposed to the strategy. See GLOBAL HIV PREVENTION WORKING GROUP, *Global Mobilization for HIV Prevention: A Blueprint for Action*, 1 SEATTLE J. FOR SOC. JUST. 297, 336 (2002); see also HUMAN RIGHTS WATCH, *Courage in the Face of Death: The Thai Drug Users' Network*, July 13, 2004, available at http://hrw.org/english/docs/2004/07/13/thaila9053_txt.htm.

¹⁸³ See HUMAN RIGHTS WATCH, *supra* note 26 at 28.

¹⁸⁴ *Id.*

¹⁸⁵ Aphaluck Bhatiasevi, *War On Drugs Raises AIDS Risk*, BANGKOK POST, July 8, 2003.

¹⁸⁶ See HUMAN RIGHTS WATCH, *supra* note 26, at 1.

¹⁸⁷ See HUMAN RIGHTS WATCH, *supra* note 26, at 1,9; cf. TASK FORCE ON DRUG USE AND HIV VULNERABILITY, UNAIDS, *Drug Use and HIV Vulnerability: Policy Research Study in Asia* 181, (2000), available at http://www.unaids.org/html/pub/publications/irc-pub01/jc395-druguse&vuln_en_pdf.pdf.

¹⁸⁸ See HUMAN RIGHTS WATCH, *supra* note 26, at 23.

Thai policies that coerce drug users into treatment and rehabilitation through threats of arrest or death compromised the voluntariness of injection drug users who participated in the AIDSVAX trials. After a group of AIDS researchers presented their findings at the Ninth National Conference on AIDS in Bangkok in July 2003, Thai police raided the researchers' offices in Chiang Mai and demanded to know the location of the study participants.¹⁸⁹ While many Thais avoid drug treatment for fear of being identified as a drug user and targeted for arrest, "scores of Thais—some drug users, some not—reported for drug treatment during the war on drugs simply because they perceived it was the only way to avoid arrest and possible murder."¹⁹⁰ Drug users who are able to prove their enrollment in a drug treatment program may be able to avoid harassment by the police.¹⁹¹ Given the authoritarian mechanisms used by the Thai government to ensure compliance with drug treatment programs, injection drug users were probably fearful of *not* participating in the HIV clinical trials. Drug users who enrolled in government-approved vaccine clinical trials to avoid persecution by government officials have not freely consented to participate.

While social and political factors contributed heavily to the lack of voluntariness among research participants, the prospect of free health care or improved access to care can create strong inducements to participate.¹⁹² For many Thai injection drug users, participating in research may be their only way to access health care. Under these conditions, subjects may believe that any benefit is worth the risk, no matter how unlikely it is that participation will confer health benefits.¹⁹³ One study of Thai trial participants concluded that principal motivations for enrolling in the study included HIV testing, a physical examination, HIV information, and altruistic reasons (e.g., to stop the spread of HIV).¹⁹⁴ In addition, economic incentives also played a role in the subjects' decisions to participate, given that seventy-two percent thought that being reimbursed for their time and travel was an incentive to participate.¹⁹⁵

¹⁸⁹ See *id.* at 39. One researcher related that the police officers "pretty much wanted to know why we were in touch with drug users and where they were...." *Id.*

¹⁹⁰ *Id.* at 32.

¹⁹¹ Human Rights Watch interviewed a thirty-six year old man who had been injecting heroin for ten years: "[i]f they [the police] see me, I present a card as proof that I'm in treatment at a medical center....If you have an ID showing you attend treatment, you are considered a 'patient,' so they don't arrest you." *Id.* at 33.

¹⁹² See Lertsithichai, *supra* note 153, at 1255.

¹⁹³ See Page, *supra* note 31, at 655 ("This is particularly true where the research involves an intervention aimed at HIV/AIDS or other deadly diseases").

¹⁹⁴ See Vanichseni *supra* note 162, at 313.

¹⁹⁵ *Id.* at 313-14.

The existence of incentives does not necessarily indicate that research subjects are being exploited.¹⁹⁶ While drug users may be induced to enroll in trials by the promise of free health services, they may be even more influenced by the “negative attitudes held against them by officials and researchers” who ran the trials, particularly the Bangkok Metropolitan Administration.¹⁹⁷ The health benefits of trial participation raised questions about undue inducement, but the more pressing reason to question the voluntariness of research subjects was the coercive political environment for injection drug users during the vaccine trial. If the informed consent and autonomy of research subjects cannot be assured amid the environment of persecution and coercion in Thailand, then U.S. companies should not conduct clinical trials in Thailand.

B. Institutional Review Boards Failed to Adequately Protect Human Subjects in Thailand

Members of the IRBs that reviewed the protocols for the AIDS VAX vaccine trials failed to properly consider the vulnerability of the subject population and the implications for informed consent. In particular, ethical review committees did not question the obvious differences in the selection criteria used for the U.S. trials and the criteria used for the Thai trials. When some or all of the subjects are vulnerable to coercion or undue influence, as with a population of injection drug users, IRBs should ensure that “additional safeguards have been included in the study to protect the rights and welfare of these subjects.”¹⁹⁸

Ethical review by an IRB located in the United States ensures that U.S. standards and regulations for protecting human research subjects are maintained when research is conducted abroad.¹⁹⁹ It is particularly important for the IRB to determine “whether conducting a research study in a developing country, rather than in the U.S. or another industrialized country, is justified.”²⁰⁰ Determining the appropriateness of a study to be conducted in a developing country may be more difficult for IRBs in

¹⁹⁶ See MACKLIN, *supra* note 34, at 127.

¹⁹⁷ See *Between the Lines*, *supra* note 176.

¹⁹⁸ Susan J. Delano, *Research Involving Adults with Decisional Impairment*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 389 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

¹⁹⁹ See Page, *supra* note 31, at 652. “It is ludicrous to hold that there are Western ethical imperatives that apply only to the West...and Asian ethical principles that apply only to that part of the world. Maintaining the same ethical standards for research will not thwart the research enterprise, but can help to ensure that judgments made at some future time will not condemn the current era as one that accepted and even endorsed double standards of research ethics.” MACKLIN, *supra* note 34, at 260.

²⁰⁰ Page, *supra* note 31, at 653.

developed countries, who are often “unfamiliar with the host country language, culture, social and ethical norms, level of health care, and other factors essential for a thorough ethical review of a clinical protocol.”²⁰¹ Researchers in developing countries have expressed concerns that U.S. IRBs lack familiarity with research conditions in developing countries.²⁰² As ethical review has become standardized under U.S. regulations, researchers suggest that the content of that review often focuses on the form and documentation of informed consent rather than the quality and substance of the consent process.²⁰³ When IRB members are less familiar with the research conditions of clinical trials in developing countries, it is particularly important to scrutinize the process of informed consent.

For international research subject to U.S. regulation, prior independent ethical review generally involves review by committees in the United States and in the country where the research will be conducted. For the AIDS VAX clinical trials, IRBs in Thailand reviewed the research proposal.²⁰⁴ Review by a Thai IRB was important for taking the local perspective into account. However, the infrastructure for ethical review is not as well-developed²⁰⁵ in Thailand as it is in the United States.²⁰⁶

The need for additional protections for drug users correlates with their capacity to give valid informed consent. It is doubtful whether voluntary consent can be assured, given the coercive social environment in Thailand. Considering the special vulnerabilities of injection drug users in Thailand, and the challenges of procuring valid informed consent from this population, IRB members should have questioned the decision to study the HIV vaccine exclusively in this population. IRB members initially failed to appreciate the coercive social environment endured by injection drug users in Thailand, but the committees also failed to suspend the study upon learning of the unsuitable conditions.

²⁰¹ Daniel W. Fitzgerald et al., *Ten Questions Institutional Review Boards Should Ask when Reviewing International Clinical Research Protocols*, 25 IRB: ETHICS & HUMAN RESEARCH 14 (2003).

²⁰² See Nancy Kass et al., *Ethical Oversight of Research in Developing Countries*, 25 IRB: ETHICS & HUMAN RESEARCH 1, 3 (2003).

²⁰³ *Id.* at 3, 8.

²⁰⁴ See AIDSINFO Phase III, *supra* note 16.

²⁰⁵ In less developed countries, investigators have “limited experience with U.S. sponsored clinical studies, potential research participants are unfamiliar with concepts such as informed consent, and institutions have not established strong human-subjects protection programs.” David A. Borasky, *International Research*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 481 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

²⁰⁶ See Page, *supra* note 31, at 652.

V. THE UNITED STATES AND THAILAND MUST IMPLEMENT LEGISLATION TO ENFORCE PROTECTIONS FOR HUMAN SUBJECTS

The compelling scientific incentives for studying HIV vaccines in Thai injection drug users must be balanced against the legal and ethical risks for the subject population. Mechanisms such as informed consent and prospective review by IRBs have evolved to protect human subjects of clinical research.²⁰⁷ However, laws and principles can only protect human subjects to the extent that they are enforced. At the time of the AIDS VAX clinical trials, social and political conditions in Thailand were not conducive to safeguarding the rights of a study population comprised of injection drug users. When there is a risk that legal and ethical protections may not function effectively in a particular study population, the research protocol must be closely scrutinized by IRBs in the host and the sponsoring countries. The existing system of IRB review in the United States must be strengthened so that research will be suspended when freely-given informed consent cannot be obtained in a population of research subjects.

Unlike the United States, Thailand has not enacted formal legislation on human experimentation.²⁰⁸ Therefore, while the recommendations proposed here may be of interest, Thailand's immediate goal should be to enact an updated version of the draft legislation that has lain dormant in Thailand since 1993.²⁰⁹ However, by examining protections currently in force in the United States, as well as proposed improvements to those protections, the Thai government can incorporate the successful aspects of the U.S. protections into a system appropriate for Thailand.

A. *Congress Should Extend the Common Rule to Govern All Research Conducted on Human Subjects*

Congress should enact laws to strengthen existing research protections in the United States. In order to resolve questions about the applicability of the Common Rule to private research conducted by companies, Congress should broaden the reach of the federal regulations.²¹⁰ One possible solution to these questions would be to extend the application of the Common Rule to all research conducted on human subjects, regardless of the sponsor. Representatives Diana L. DeGette (D-CO) and Jim Greenwood (R-PA) advocated for this change when they introduced the Human Research

²⁰⁷ *Id.* at 652-53.

²⁰⁸ *See A Poison Pill?*, *supra* note 42.

²⁰⁹ *See id.* (the final draft of the legislation was never proposed to the Thai Parliament).

²¹⁰ *See* INSTITUTE OF MEDICINE, *supra* note 36, at 198.

Subject Protections Act of 2002.²¹¹ The bill sought to extend federal protections to all research involving human subjects, including research that is not federally funded.²¹² Soon after the bill was introduced in the House, Senator Edward Kennedy (D-MA) introduced a similar bill in the Senate.²¹³ Both bills died in Committee, and while a similar bill was subsequently introduced, it was not enacted into law.²¹⁴

Congress should act quickly to extend the protections of the federal regulations to all research participants, in order to keep pace with the increasingly private nature of clinical research. Even if Congress extends the federal regulations to all sponsors located within the United States, the laws would be more effective if countries such as Thailand enact similar legislation.

B. Gaps in the Existing U.S. Regulations Must Be Bridged and Inconsistencies Should Be Harmonized

One major structural problem with the U.S. system of protections for human subjects is the disconnect between the federal regulations and their underlying ethical foundations. IRBs must evaluate laws, institutional regulations, and standards of professional practice against ethical principles to answer practical questions about proposed research.²¹⁵ The two most important sources of guidance that IRBs consider are the federal regulations and the Belmont Report.²¹⁶ Although both the federal regulations and the ethical principles of the Belmont Report are designed to protect human subjects, a gap between the two authorities has led to poor IRB decisionmaking in cases such as the AIDSVAX trials. Problems arise because the federal regulations and ethical guidance documents do not directly reference each other. For example, the Code of Federal Regulations barely mentions ethics, or the role that ethical principles play in protecting human subjects.²¹⁷ The Belmont Report enumerates “ethical principles and applications without specifying how they relate to interpreting and applying

²¹¹ Human Subject Research Protections Act of 2002, H.R. 4697, 107th Cong. (2002).

²¹² *Id.* at § 491A(a).

²¹³ See Research Revitalization Act of 2002, S. 3060, 107th Cong. § 491(b) (2002).

²¹⁴ See Protection for Participants in Research Act of 2003, H.R. 3594, 108th Cong. § 491A(a) (2003).

²¹⁵ See Harold Y. Vanderpool, *An Ethics Primer for IRBs*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION 3 (Robert J. Amdur & Elizabeth A. Bankert eds., 2002).

²¹⁶ *Id.*

²¹⁷ *Id.*

federal regulatory rules.”²¹⁸ As a result, “there is a lack of national guidance on the...ethical requirements of providing adequate protections” for human subjects.²¹⁹

Greater educational training for IRB members in research ethics would improve the current structural problems.²²⁰ When IRB members are familiar with the ethical issues specific to international research, they will be better equipped to grapple with substantive issues, as opposed to merely focusing on the procedural requirements of the federal regulations.²²¹ The tendency of IRBs to focus on the documentation of informed consent undermines the widely accepted notion that consent is a process.²²² While the consent document serves as a physical representation of an exchange between researcher and subject, it may be more important to focus on whether the informed consent provisions are achievable in a given social context and within a particular population. The focus of the consent process should be on informing and protecting participants, and not on protecting institutions.²²³

While the provisions of the Common Rule are nearly identical to the provisions of the FDA regulations, the existence of two separate sets of rules creates another area of inconsistency in the protections. The proposed Human Research Subject Protections Act of 2002, as well as the subsequent Protection for Participants in Research Act of 2003, sought to harmonize the federal regulations.²²⁴ Both bills proposed a study of the differences between the two statutes, and required that differences in subsequent rulemaking be justified.²²⁵ Minimizing the gaps between law and ethics and harmonizing the federal regulations is necessary for a more efficient and effective administration of the laws.

²¹⁸ *Id.* Ruth Macklin notes that “Leading controversies in research ethics can be traced to this confusion between ethical principles and specific rules of procedure, in particular, rules governing the informed consent process and the need for prior review of research by an independent committee.” MACKLIN, *supra* note 34, at 147.

²¹⁹ INSTITUTE OF MEDICINE, *supra* note 36, at 39.

²²⁰ *See* Emanuel, *supra* note 3, at 283.

²²¹ *See* Kass, *supra* note 202, at 9; *see also* INSTITUTE OF MEDICINE, *supra* note 36, at 113-114 (proposing research ethics education goals).

²²² *See* Emanuel, *supra* note 3, at 286.

²²³ *See* INSTITUTE OF MEDICINE, *supra* note 36, at 92.

²²⁴ *See generally* Human Subject Research Protections Act of 2002, H.R. 4697, 107th Cong. (2002); Protection for Participants in Research Act of 2003, H.R. 3594, 108th Cong. (2003) (the bills would require the Secretary of Health and Human Services to review and harmonize the federal regulations).

²²⁵ *See* Human Subject Research Protections Act of 2002, H.R. 4697, 107th Cong. § 491A(b)(2) (2002); Protection for Participants in Research Act of 2003, H.R. 3594, 108th Cong. § 491A(b)(2) (2003).

C. *Accreditation Programs Would Promote Effective Oversight of Research on Human Subjects*

Accreditation programs for IRBs would be a powerful tool for accelerating and maintaining improvement in the provision of research protections to participants.²²⁶ At the very least, accreditation would help to ensure that IRBs conduct self-assessments and address deficiencies.²²⁷ The Council for Certification of IRB Professionals has begun offering credentialing programs, which could streamline review and improve continuing review.²²⁸ The proposed Human Research Subject Protections Act of 2002 would have made accreditation of IRBs voluntary, while the Research Revitalization Act of 2002 would have imposed mandatory accreditation.²²⁹ The Institute of Medicine²³⁰ advises that accreditation is currently “a nascent process that will require substantial time and development before a meaningful assessment of its added value can be made.”²³¹

D. *Reviewing Committees in the United States Need Greater Familiarity with the Local Context of Research Conducted Abroad*

IRBs are charged with ensuring that informed consent is obtained from research participants in diverse communities. The Office for Human Research Protections (“OHRP”), which monitors IRBs in the United States, “expects the designated IRB to have knowledge of the local research context.”²³² In the case of HIV vaccine research conducted in the United States and Thailand, the characteristics of the sponsor and host countries varied greatly. IRBs located outside of the host country should be provided with basic information about economic and political realities in the host country.²³³ In the case of international clinical trials, the responsibility for ensuring IRB familiarity with the research context should rest with both the

²²⁶ See INSTITUTE OF MEDICINE, *supra* note 36, at 177.

²²⁷ *Id.* at 171.

²²⁸ See Emanuel, *supra* note 3, at 287. Other accreditation organizations include the Association for Accreditation of Human Research Protection Programs, and the National Committee for Quality Assurance. INSTITUTE OF MEDICINE, *supra* note 36, at 171.

²²⁹ See Human Subject Research Protections Act of 2002, H.R. 4697, 107th Cong. § 491A(e)(5) (2002); Research Revitalization Act of 2002, S. 3060, 107th Cong. § 491(d) (2002).

²³⁰ “The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public . . .” INSTITUTE OF MEDICINE, *supra* note 36, at *iv*.

²³¹ INSTITUTE OF MEDICINE, *supra* note 36, at 175.

²³² Borasky, *supra* note 205, at 481. Available evidence suggests that U.S. IRBs rarely try to communicate with host-country ethics review committees. MACKLIN, *supra* note 34, at 152.

²³³ See Kass, *supra* note 202, at 9.

host and sponsoring countries. Particularly for higher-risk research, such as HIV vaccine trials, a consultant familiar with Thai culture should be added to the U.S. IRB, and it may be necessary for some IRB members to regularly visit the research site.²³⁴

E. Thailand and the United States Should Engage in Mutually Beneficial Research Collaboration

While many aspects of the protections for human subjects are ripe for improvement, collaboration between the United States and Thailand should continue. Both the United States and Thailand gain valuable scientific knowledge from clinical trials. Additionally, Thailand receives derivative benefits from the “capacity building²³⁵ of its scientists, researchers and health personnel, and infrastructure strengthening of laboratory and specimen archiving.”²³⁶ Both the CIOMS guidelines and the UNAIDS guidance document assert that capacity building in host countries is an ethical component of research.²³⁷ Capacity building in Thailand is of particular value because Thailand continues to host vaccine clinical trials. Another Phase III trial is already underway in Thailand, testing a combination of HIV vaccines in 16,000 volunteers.²³⁸ Unlike the VaxGen study²³⁹ analyzed in this Comment, which exclusively recruited injection drug users, the current study follows a more general population of volunteers.²⁴⁰ As a case study, the VaxGen AIDSVAX clinical trials can

²³⁴ Borasky, *supra* note 205, at 481.

²³⁵ Research capacity development is defined as the “process by which individuals, organizations, institutions and societies develop abilities (individually and collectively) to perform functions effectively, efficiently and in a sustainable manner to solve problems.” GLOBAL FORUM FOR HEALTH RESEARCH, *The 10/90 Report on Health Research 2001-2002* x (2002), <http://www.globalforumhealth.org/filesupld/35.pdf>.

²³⁶ Alice Page, *Prior Agreements in International Clinical Trials: Ensuring the Benefits of Research to Developing Countries*, 3 YALE J. HEALTH POL’Y, L. & ETHICS 35, 40-41 (2002); see Ministry Insists on Continuing Vaccine Trials Despite Criticism, BANGKOK POST, Jan. 21, 2004 (describing post-trial benefits to Thailand).

²³⁷ See CIOMS Guidelines, *supra* note 78, Commentary on Guideline 20 (“In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research”); UNAIDS Guidance Document, *supra* note 82, at 15 (“Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process”).

²³⁸ AIDS VACCINE CLEARINGHOUSE, *supra* note 27.

²³⁹ CLINICALTRIALS.GOV, *Effectiveness of AIDSVAX B/E Vaccine in Intravenous Drug Users in Bangkok, Thailand*, *supra* note 26.

²⁴⁰ See Maugh, *supra* note 25, at 6.

provide useful information for planning future preventative HIV vaccine trials.

VI. CONCLUSION

If the United States and Thailand continue to collaborate in the search for an HIV vaccine, the protections for human subjects that exist in the United States must be equally robust when applied in Thailand. In the VaxGen clinical trials conducted in Thailand, the provision of informed consent and IRB review failed to provide the level of protection espoused by the Belmont Report and required by U.S. federal regulations.

Given the special vulnerabilities of injection drug users in Thailand and the challenges of procuring valid informed consent from this population, IRBs should have questioned the decision to study the HIV vaccine exclusively in this population. Even if IRBs initially failed to appreciate the coerciveness of the social environment for injection drug users in Thailand, the committees should have suspended the study upon learning of the conditions. In the future, U.S. pharmaceutical companies conducting research on vulnerable populations abroad must be held to the same standards that apply in their home country, and steps must be taken to ensure that federal regulations are ethically implemented in practice. To strengthen the protections for human subjects, Thailand should enact comprehensive national legislation, and existing legislative protections in the United States should be expanded to reflect the increasingly international scope of biomedical research.