

NOTES

FITTING A SQUARE PEG INTO A ROUND HOLE?: IMPOSING INFORMED CONSENT AND POST-TRIAL OBLIGATIONS ON UNITED STATES SPONSORED CLINICAL TRIALS IN DEVELOPING COUNTRIES

ESTHER CHANG*

I. INTRODUCTION

A rural Chinese province recently reported a nearly forty percent increase in *H. Pylori* bacterium infections after a 1994 National Cancer Institute (“NCI”) study was conducted in the region.¹ The study began in 1988 after the NCI partnered with Chinese researchers to: (1) determine the prevalence of *H. Pylori* bacteria, the leading cause of stomach ulcers and a risk-raising factor for stomach cancer, and (2) discover whether dietary supplements could successfully prevent these infections.² Unbeknownst to the NCI, Chinese research standards changed in 1991.³ The endoscopes used to collect stomach samples from study participants were wiped off with antiseptic rather than soaked and sterilized after each exam.⁴ When news of the outbreak came to light, scientists disagreed over the manner in which study participants should be informed. The Chinese maintained that the infection’s origin was unknown, whereas the NCI wanted to acknowledge the infection’s probable correlation with study participation.⁵

* J.D. candidate, University of Southern California Law School, 2002; B.S., Dartmouth University, 1997. I would like to thank Professor Alexander Capron for his guidance, the 2001–2002 ILJ Board and staff for their hard work and dedication, Sheila Arriola for spending so many thankless hours on this year’s ILJ issues, and finally, to my beloved friends and family for their love and support.

¹ See Marilyn Marchione, *Hundreds in China May Have Gotten Infection from Scientific Study: Ethics Commission Cites Case As an Example of Problems with Research Overseas*, MILWAUKEE J. SENTINEL, May 11, 2000, 2000 WL 3857944.

² *Id.*

³ *Id.*

⁴ *Id.*

⁵ *Id.*

The NCI study exemplifies some of the dilemmas U.S. researchers face when they conduct studies in countries with differing medical standards, and ethical, economic, political, and cultural perspectives. Despite these conflicts, in December of 2000, the National Institute of Health (“NIH”) unveiled a one hundred million dollar AIDS initiative to expand funding for clinical research in developing nations like Uganda, Thailand, South Africa, the Dominican Republic, and Kenya.⁶ Given the increasing number of U.S. sponsored overseas research projects, what legal safeguards exist to ensure that foreign research subjects are adequately protected?

To address this question and other bioethical issues in human research, former President Clinton organized the National Bioethics Advisory Commission (“NBAC”).⁷ The presidential panel’s September 2000 report⁸ endorses a medley of regulatory obligations for U.S. researchers prior to, during, and upon completion of a clinical trial in a developing country. The NBAC recommendations reaffirm the importance of substantive informed consent, but grant researchers the flexibility to modify impractical procedures in foreign-based studies.⁹ The proposal also suggests promulgating post-trial obligations on researchers and research sponsors, including the continuation of successful investigational treatments or the initiation of alternative benefits for research subjects and host populations.¹⁰

In this note, I first submit that NBAC’s informed consent regulations set commendable standards for our scientists to strive towards and should be adopted. Informed consent as it stands now, however, fails to address the informational, financial, and political imbalance between U.S. researchers and foreign research subjects. In addition, adherence to U.S. regulations by overseas researchers is hard to measure, monitor, and enforce out on the field. Second, while NBAC’s proposed post-trial regulations attempt to create additional protections for foreign research subjects, they are more effective when they act in conjunction with legislated financial incentives. Given that most researchers lack the resources to effectuate NBAC’s proposed post-trial obligations, legislated incentives better encourage research sponsors to step forward, subsidize post-trial programs, assist in technology transfer, and help host countries build their own research and manufacturing capabilities.

⁶ See *Plan Aims to Prevent Spread of HIV Worldwide; \$100 Million Dedicated to Research in Poor Nations*, MILWAUKEE J. SENTINEL, Dec. 3, 2000, at 27A, available at LEXIS, News Library, MILJNL File [hereinafter *Plan Aims to Prevent Spread of HIV Worldwide*].

⁷ Exec. Order No. 12,975, 60 Fed. Reg. 52,063 (Oct. 3, 1995). The NBAC’s charter expired on October 3, 2001, but its reports still provide guiding authority in the medical trial community. See National Bioethics Advisory Commission, at <http://www.georgetown.edu/research/nrcbl/nbac/> (last visited November 18, 2002).

⁸ NAT’L BIOETHICS ADVISORY COMM’N, ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES (2001), available at <http://www.bioethics.gov> [hereinafter NBAC]. The NBAC report focuses on clinical trials located in developing countries that are subject to U.S. regulations. *Id.* at ii.

⁹ *Id.* at 38. See also Gretchen Vogel, *Panel Proposes Rules for Research Abroad*, 290 SCI. 28 (2000).

¹⁰ NBAC, *supra* note 8, at 74. See also Vogel, *supra* note 9, at 28.

To facilitate an investigation of this topic, the progression of this note runs as follows: first, an introduction on clinical trials and why they are increasingly executed overseas; next, an examination of present informed consent regulations in comparison to NBAC's recommendations; and finally, a dissection of the efficacy of NBAC's proposed post-trial obligations.

For purposes of this note, "exploitation" will be defined as "an unjust or improper use of another person for one's own profit or advantage."¹¹ Hereinafter, "subject(s)" will refer to human research participants. Lastly, "informed consent" refers to the process by which scientists disclose all the relevant study information to the subjects, and subjects *voluntary* consent to enrollment after considering the disclosed information.¹²

II. BACKGROUND: CLINICAL STUDIES AND THE DRUG APPROVAL PROCESS

In the United States, substantial evidence of a drug's safety and efficacy through clinical trials is a necessary prerequisite in obtaining the Food and Drug Administration's ("FDA") approval for drug marketing.¹³ Clinical trials occur after laboratory chemical and animal tests reveal palliative potential in an investigational drug or therapy. There are four basic clinical phases. In Phase I, scientists examine the safety of the experimental drug or therapy by identifying metabolic, pharmacologic, and toxicologic effects for the first time on a group of twenty to eighty people.¹⁴ In Phase II, the investigational drug or therapy is tested in controlled studies against placebos or standard treatments on larger groups of 100 to 300 people.¹⁵ Further data processing and gathering in Phase III research occurs on study groups as large as 3,000 people.¹⁶ Much of the detailed analysis on the side effects, dosage, and effectiveness in Phase III studies are then reported to the FDA for the filing of a "New Drug Application."¹⁷ Finally, a new drug or treatment begins Phase IV testing after FDA authorization is granted, but further monitoring of human subjects is necessary to reveal any long-term side effects.¹⁸

U.S. government agencies and drug manufacturers seeking to conduct foreign clinical trials are subject to the Department of Health and Human Services' ("DHHS") Federal Policy for the Protection of Human Subjects¹⁹

¹¹ See WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY UNABRIDGED 801-02 (1993).

¹² See generally JESSICA W. BERG, PAUL S. APPELBAUM, CHARLES W. LIDZ, & LISA S. PARKER, INFORMED CONSENT (2d ed. 2001) (discussing the various definitions, goals, and perspectives regarding informed consent).

¹³ See 21 U.S.C. § 355(a) (2000).

¹⁴ E.g., Nat'l Inst. of Health, *What Is a Clinical Trial?*, at <http://www.clinicaltrials.gov/ct> (last visited Apr. 5, 2002) [hereinafter NIH].

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ Protection of Human Subjects, 45 C.F.R. § 46 (2001). The Federal Policy applies to research conducted, supported, or regulated by DHHS. See OFFICE FOR PROTECTION FROM RESEARCH RISKS, NIH, PROTECTING HUMAN RESEARCH SUBJECTS: INSTITUTIONAL REVIEW BOARD GUIDEBOOK 2-1

and FDA regulations.²⁰ U.S. scientists bound by these regulations must ensure that research subjects receive adequate disclosure and voluntarily consent to participate, the study holds a favorable risk to benefit ratio for subjects, and the study fairly distributes the benefits and the burdens from its undertaking.²¹ In addition, all clinical trials governed under federal jurisdiction must be examined and approved by a U.S. Institutional Review Board (“IRB”)²² prior to commencement.²³

III. PROS AND CONS OF CONDUCTING U.S. CLINICAL TRIALS IN DEVELOPING COUNTRIES

The increase in U.S. sponsored clinical trials conducted in developing countries is attributable to a number of factors. First, clinical trials are more effective when scientists can successfully recruit a statistically significant sample size.²⁴ This task is easier to accomplish in areas with a higher prevalence of the researched disease, infection, or condition. For example, the World Health Organization (“WHO”) estimates that sixty-five percent of the world’s HIV-infected population resides in sub-Saharan Africa.²⁵ Accordingly, an increasing number of HIV/AIDS clinical trials have been conducted in Africa over the past decade.²⁶ Second, testing in developing countries can be cheaper and more efficient.²⁷ For example, U.S. medical standards dictate that tuberculosis (“TB”) patients should be treated with prophylaxis regimens.²⁸ In contrast, local standards in developing countries leave TB patients with few treatment options. Thus, overseas placebo-controlled studies of TB infections may avoid the expense of costlier baseline treatments (e.g., prophylaxis) that would otherwise be required for U.S. domestic trials. These studies may also cut down on costs by providing statistically significant outcomes in a shorter

(1993) [hereinafter OPRR]. To create uniformity in human research, the same policy has also been adopted by fifteen other federal departments and agencies, including the National Science Foundation. *Id.*

²⁰ See 21 C.F.R. § 50 (2001). See also 21 C.F.R. § 56 (2001).

²¹ 45 C.F.R. §46.111, 46.116 (2001). See also NBAC, *supra* note 8, at 13.

²² Institutions engaged in research with federal departments or agencies must establish an Institutional Review Board (“IRB”). OPRR, *supra* note 19, at 1-1, 2-1. IRBs are independent administrative bodies commissioned to protect human research participants and have “the authority to approve, require modifications in, or disapprove” projects that fail to comply with federal regulations or institutional policies. *Id.* See generally BOWEN HOSFORD, BIOETHICS COMMITTEES 35–45 (1986).

²³ See 45 C.F.R. § 46.109 (2001). Some developing countries also have ethics committees to review U.S. research projects conducted in their respective countries. NBAC, *supra* note 8, at 13. See Eldryd Parry, *The Ethics of Clinical Research in Developing Countries*, 34 J. ROYAL C. PHYSICIANS LONDON 328 (2000).

²⁴ See NBAC, *supra* note 8, at 7.

²⁵ Gernard I. Msamanga & Wafaie W. Fawzi, *The Double Burden of HIV Infection and Tuberculosis in Sub-Saharan Africa*, 337 NEW ENG. J. MED. 849, 849 (1997).

²⁶ E.g., Julian Borger, *Dying for Drugs: Volunteers or Victims? Concern Grows over Control of Drug Trials*, GUARDIAN (London), Feb. 14, 2001, at 4, available at LEXIS, News Library, GUARDN File.

²⁷ NBAC, *supra* note 8, at 7; Margaret Wertheim, *Medical Sweatshops: The Third World Is Providing a Cheap Source of Subjects for Research into AIDS and Other Conditions*, GUARDIAN (London), Oct. 5, 2000, at 3, available at LEXIS, News Library, GUARDN File.

²⁸ Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 NEW ENG. J. MED. 847, 848 (1997).

time period.²⁹ Furthermore, investigators may avoid some of the pre-trial bureaucracy found in countries like the United States that substantially delay the commencement of clinical studies.³⁰ Third, researching abroad may be necessary in countries that require domestic testing prior to drug marketing approval.³¹ Fourth, a host country may actively seek out U.S. collaboration on interventions for indigenous health problems.³² Some countries cannot afford the standard medical treatments of wealthier nations and seek to discover cheaper, effective alternatives that can be practically initiated under their own economic and cultural circumstances.

Despite the apparent advantages of conducting research in developing countries, there are also significant concerns. First, cultural and linguistic barriers may prevent U.S. required informed consent provisions from being effectively applied in foreign contexts.³³ Second, victims in developing countries have few legal recourses against U.S. researchers and study sponsors when harm results from a study. Potential plaintiffs suing U.S. researchers under the Alien Tort Claims Act (“ACTA”) face tremendous obstacles in proving that investigators contravened customary human rights norms.³⁴ The costs of engaging in an international court battle may be prohibitive. Moreover, current federal court trends make it unlikely that ACTA will be expanded to cover the scope of bioethical violations.³⁵ Third, some scientists contend that the medical and legal term “standard of care” is misapplied when it is used to justify the adoption of indigenous treatments in study designs.³⁶ They argue that local treatments bear little correlation with acceptable, chosen “standard of care” measures, but rather correlate to the inability of the local population to afford or access care.³⁷ Thus, the “standard of care” justification manipulates unacceptable U.S. research risks into acceptable risks in foreign contexts, especially when large disparities in health resources exist between the United States and the host country. This situation is most evident in the debate over placebo-controlled trials.

In 1997, a number of scientists began to publicly criticize a series of randomized, placebo-controlled HIV trials conducted in Africa, Thailand, and the Dominican Republic.³⁸ These studies investigated whether the

²⁹ Eliot Marshall, *Controversial Trial Offers Hopeful Result*, 279 SCI. 1299, 1299 (1998).

³⁰ See Mary Pat Flaherty, Deborah Nelson, & Joe Stephens, *Testing Tidal Wave Hits Overseas; on Distant Shores, Drug Firms Avoid Delays—and Scrutiny*, WASH. POST, Dec. 18, 2000, at A1, available at LEXIS, News Library, WPOST File. See also NBAC, *supra* note 8, at 7.

³¹ See NBAC, *supra* note 8, at 7.

³² *Id.*

³³ *Id.* at 38–42. See also BERG ET AL., *supra* note 12, at 311–13.

³⁴ See Jonathan Todres, *Can Research Subjects of Clinical Trials in Developing Countries Sue Physician-Investigators for Human Rights Violations?*, 16 N.Y.L. SCH. J. HUM. RTS. 737, 766 (2000).

³⁵ *Id.*

³⁶ See Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW ENG. J. MED. 853, 855 (1997).

³⁷ *Id.*

³⁸ Jay Dyckman, *The Myth of Informed Consent: An Analysis of the Doctrine of Informed Consent and Its (Mis)application in HIV Experiments on Pregnant Women in Developing Countries*, 9 COLUM. J. GENDER & L. 91, 93 (1999); Lurie & Wolfe, *supra* note 36, at 853. But see Joseph Saba & Arthur

short-term administration of the antiretroviral drug, zidovudine, to women during labor reduced infant HIV transmission.³⁹ The NIH, Center for Disease Control (“CDC”), and WHO argued that the placebo-control design best answered the question “Is the shorter [zidovudine] regimen better than nothing?”⁴⁰ They maintained that impoverished countries had little means of benefiting from studies that failed to account for the local “standard of care” (which could be meager or non-existent).⁴¹ Unlike studies offering unlimited access to expensive drugs, placebo-controlled studies arguably offered hope that positive outcomes could be practically reapplied to the host setting. Supporters of the studies also insisted that accurate answers could not have been extracted in such a short time period (one to two years) without the placebo design.⁴²

Critics, however, insist that scientists could have organized an equivalency study giving groups of women varying doses of zidovudine, and comparing the results to already proven levels of the drug’s effectiveness.⁴³ Instead of analyzing the drug against no treatment, scientists could have inquired into the possibility of administering less zidovudine without compromising the perinatal HIV transmission rate.⁴⁴ Evaluating the study in this manner may have offered each woman hope of decreasing their baby’s HIV infection risk, while providing informative results. As illustrated in this example, the variance in both practice and views on the proper ethical standards in foreign clinical trials demonstrates that no consensus exists.

IV. INFORMED CONSENT: PROTECTING SUBJECTS IN HUMAN RESEARCH

The potential exploitation of research subjects in developing countries underscores the importance of embedding protective mechanisms for subjects in the study design. One historically utilized protective measure has been the required procurement of informed consent. This note will now examine the history of informed consent before pursuing a comparison of the doctrine with NBAC’s proposed recommendations.

A. HISTORY OF INFORMED CONSENT

Our modern informed consent doctrine traces its origins to the aftermath of World War II and the conviction of Nazi researchers responsible for “murders, tortures, and other atrocities committed in the

Amman, *A Cultural Divide on AIDS Research*, N.Y. TIMES, Sept. 20, 1997, at A15, available at LEXIS, News Library, NYT file.

³⁹ See Lurie & Wolfe, *supra* note 36, at 854.

⁴⁰ *Id.*

⁴¹ See Burton Bollag, *Should Western Research Ethics Apply to Fighting AIDS in Africa*, CHRON. OF HIGHER EDUC., July 7, 2000, at A41, available at LEXIS, News Library, CHEDUC File; Charles W. Henderson, *Ethics CDC Explains Its Stand on Controversial Third World AZT Study*, AIDS WEEKLY PLUS, July 28, 1997, 1997 WL 11006847.

⁴² Henderson, *supra* note 41.

⁴³ Lurie & Wolfe, *supra* note 36, at 854.

⁴⁴ *Id.*

name of medical science.”⁴⁵ Each Nazi experiment was conducted without the subject’s informed consent, and designed with death as the inevitable consequence. Some prisoners froze to death in studies documenting the progression of hypothermia.⁴⁶ Others suffocated on behalf of high-altitude research.⁴⁷ Even more were injected with malaria, cholera, smallpox, or typhus in attempts to discover new vaccines.⁴⁸ Although the majority of Nazi experiments intended to solve the military’s legitimate medical woes, they so grossly violated basic medical and human rights norms that they prompted the creation of several important documents.

The first of these documents was the Nuremberg Code.⁴⁹ The Code’s ten basic tenets were first codified by the Allied prosecution’s medical expert, Dr. Andrew C. Ivy, and later adopted in the Nuremberg Tribunal opinion.⁵⁰ The document’s most notable provision states:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.⁵¹

This marked the first time an international court publicly recognized the right of informed disclosure and voluntary consent in medical research.⁵² The adopted stringent language, however, invoked a blanket exclusion on the participation of children and incompetent persons in experimental research.

In June of 1964, the 18th World Medical Association General Assembly adopted the Declaration of Helsinki,⁵³ which delineated and modified the ideas laid out in the Nuremberg Code. The Declaration relaxed its predecessor’s informed consent provision, allowing children and legally incompetent persons to participate in experimental treatments so long as a legal guardian consented.⁵⁴ The Declaration also provided that a subject “should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time [T]he physician

⁴⁵ See ALBERT R. JONSEN, A SHORT HISTORY OF MEDICAL ETHICS 100–02 (2000). See also George J. Annas & Michael A. Grodin, *Medical Ethics and Human Rights: Legacies of Nuremberg*, 3 HOFSTRA L. & POL’Y SYMP. 111, 112–14 (1999).

⁴⁶ See JONSEN, *supra* note 45, at 101.

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ *Id.*; 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW 181–82 (1949) [hereinafter Nuremberg Code], reprinted in OPRR, *supra* note 19, at app. A6-1.

⁵⁰ JONSEN, *supra* note 45, at 101. See also Annas & Grodin, *supra* note 45, at 112.

⁵¹ See JONSEN, *supra* note 45, at 100; Nuremberg Code, *supra* note 49, at app. A6-1.

⁵² See Todres, *supra* note 34, at 742.

⁵³ See WORLD MED. ASS’N, WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Helsinki, Finland, 1964), http://www.wma.net/e/policy/17-c_e.html.

⁵⁴ *Id.*

should then obtain the subject's freely-given informed consent, preferably in writing."⁵⁵

The Nuremberg Code and Declaration of Helsinki have never been collectively adopted by the international community.⁵⁶ Both codes of ethics, however, have played an influential role in shaping American policies, and both are referenced to in U.S. IRB procedures.

B. U.S. INFORMED CONSENT REGULATIONS APPLIED ELSEWHERE

Informed consent is legally regulated in the United States by the FDA and IRBs under title 45, section 46, and title 21, sections 50 and 56 of the Code of Federal Regulations. Present rules require disclosure of a study's purpose, descriptions of risks and benefits, information on alternative treatments, statements on confidentiality protocols, information on remedies for injuries resulting from the study, information on how to contact study liaisons, and a statement assuring that participation is voluntary and withdrawal at any time without penalty is at the discretion of the participant.⁵⁷ Intrinsic to this process is the additional requirement that subjects signify their consent through written documentation.⁵⁸ Each U.S. sponsored project conducted in a developing country must satisfy the above-mentioned regulations.

Some critics argue that transposing this Western-derived informed consent value on foreign study subjects is a show of "ethical imperialism."⁵⁹ Other researchers support the substantive idea of informed consent, but insist that U.S. dictated procedures applied in cross-cultural contexts may be awkward, uninformative, or culturally inappropriate.⁶⁰ Developing countries have different consent histories, including ones where men consent on behalf of their wives and daughters,⁶¹ or patients defer to their physician's recommendations rather than receive full disclosure about their diagnosis.⁶² Arguably, U.S. sponsored research could not be ethically carried out in those countries if informed consent were a requirement. Also, potential enrollees may walk away from studies frustrated with long informed consent statements that attempt to comply with U.S. standards. In addition, the high illiteracy rate in some countries makes the acquisition of written consent extremely cumbersome. Finally, scientists may misapply the informed consent doctrine, relegating it to the procurement of written documentation rather than a concerted effort to prepare subjects for an informed choice.

⁵⁵ See *id.* ¶ B22.

⁵⁶ Todres, *supra* note 34, at 749.

⁵⁷ 45 C.F.R. § 46.116(a) (2001). See NBAC, *supra* note 8, at 37.

⁵⁸ See 45 C.F.R. § 46.117 (2001).

⁵⁹ See Dyckman, *supra* note 38, at 103.

⁶⁰ BERG ET AL., *supra* note 12, at 311–13; Dyckman, *supra* note 38, at 103.

⁶¹ See NBAC, *supra* note 8, at 45.

⁶² See Richard R. Love & Norman C. Fost, *Ethical and Regulatory Challenges in a Randomized Control Trial of Adjuvant Treatment for Breast Cancer in Vietnam*, 45 J. INVESTIGATIVE MED. 423, 424–25 (1997).

To illustrate, in 1998, *N.Y. Times* journalist Howard French interviewed pregnant women about their reasons for enrolling in the controversial African placebo-controlled HIV trials.⁶³ Some women joined believing they were promised medical treatment.⁶⁴ Others recalled scientists assuring them that their participation would help their babies and ease childbirth.⁶⁵ Even more expressed confusion over the definition of “placebo,” or why scientists might dispense a sugar pill rather than the actual drug.⁶⁶ These misconceptions demonstrate the breakdown in the disclosure process prior to consent, and suggest that U.S. procedures may not be effectively implemented in developing countries.

C. NBAC’S INFORMED CONSENT RECOMMENDATIONS:
PROS AND CONS

NBAC’s informed consent recommendations acknowledge the legitimacy of these barriers, but insist that continuation of this informed consent tradition is a necessary defense against vigilante research. The recommendations focus on three traditional elements of informed consent: (1) providing subjects with information (e.g., the goal of study, risks, benefits, etc.), (2) ensuring that the information has been understood, and (3) ensuring that the subjects provide voluntary consent for study participation.⁶⁷ These elements are codified in NBAC’s adopted definition of “informed consent” as “a process by which an individual voluntarily expresses his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to his or her decision to participate.”⁶⁸

D. ORAL CONSENT AND PROCEDURAL MODIFICATIONS

Acquiring written consent from illiterate populations can be a challenge. The process is further complicated in areas governed by oppressive regimes, where subjects are suspicious of attaching signatures or fingerprints to documents they can’t read.⁶⁹ Acknowledging these hurdles, NBAC’s recommendations permit waivers of the written consent requirement for scientists in developing countries found in title 45, section 46.117 of the C.F.R.⁷⁰ If adopted, this recommendation opens the door to oral consent as a viable alternative.

Under the NBAC proposal, scientists can amend other impracticable procedural requirements in developing areas, so long as prior approval is granted by an IRB and audited by a competent body.⁷¹ These

⁶³ See Howard W. French, *AIDS Research in Africa: Juggling Risks and Hopes*, N.Y. TIMES, Oct. 9, 1997, at A1.

⁶⁴ *Id.*

⁶⁵ *Id.*

⁶⁶ *Id.*

⁶⁷ NBAC, *supra* note 8, at 36.

⁶⁸ *Id.* at 37.

⁶⁹ *Id.* at 49.

⁷⁰ *Id.* at 50.

⁷¹ *Id.*

recommendations allow researchers to consider the culture and lifestyle of a population with greater ease and alter the procedures when necessary. While these procedural requirements can be waived, the substantive standard of informed consent can never be compromised.⁷²

E. INFORMED CONSENT AND THERAPEUTIC MISCONCEPTION

NBAC calls for U.S. researchers to delineate plans resolving therapeutic misconceptions through informed consent.⁷³ Therapeutic misconception exists when a subject confuses the researcher-subject dynamic with a physician-patient relationship.⁷⁴ Subjects may fail to understand that a study's primary goal is not to treat or heal, but to solve scientific queries for the benefit of others. For instance, in 1996, throngs of people hit by the meningitis epidemic flocked to receive "care" from a Pfizer research team studying the disease in Nigeria.⁷⁵ According to one lab technician involved in the study, "[t]he patients did not know if it was research or not. They just knew they were sick."⁷⁶ While the NBAC recommendation theoretically protects subjects in situations like this, the actual impact of words in reconciling a subject's belief with the study's genuine purpose is still uncertain. Therapeutic misconceptions may be hard to dispel for people desperate for medical care, especially when they approach foreign studies as their only hope of getting treatment.

F. COMMUNITY OUTREACH AND CULTURAL SENSITIVITY

NBAC adopts the disclosure requirements listed in title 45, section 46.116 of the C.F.R. and emphasizes the IRB's duty to deny studies deviating from the "substantive ethical standard" of informed consent.⁷⁷ Unlike the C.F.R., NBAC requires researchers to consider cultural and community dynamics when designing the informed consent process. This consideration includes community consultations, sensitivity to local norms (e.g., approaching the community leader prior to enrollment), and collaboration with local leaders to find innovative ways to convey information.⁷⁸ In addition, NBAC requires that researchers accommodate requests to consult with religious leaders, friends, or family members.⁷⁹ Under no circumstances may another's authorization take the place of the subject's affirmative consent.⁸⁰ Further, U.S. government support of

⁷² *Id.* at 38.

⁷³ *Id.* at 48.

⁷⁴ *Id.*

⁷⁵ Joe Stephens, *Where Profits and Lives Hang in Balance; Finding an Abundance of Subjects and Lack of Oversight Abroad, Big Drug Companies Test Offshore to Speed Products to Market*, WASH. POST, Dec. 17, 2000, at A1, available at LEXIS, News Library, WPOST file.

⁷⁶ *Id.*

⁷⁷ NBAC, *supra* note 8, at 38.

⁷⁸ *Id.* at 40–42.

⁷⁹ *Id.* at 44.

⁸⁰ *Id.* at 44–45.

research in different cultural settings and dialogues on the functional implementations of informed consent is encouraged.⁸¹

On one hand, adoption of these recommendations may beneficially decrease incidences of misapplied informed consent in poorer countries. For example, Marie-Pierre Preziosi and her colleagues investigated whether substantive informed consent was achievable in a pertussis vaccine trial in rural Senegal. Between April and September of 1992, researchers and physicians gave presentations to each study village in French and Sereer.⁸² The presentations included a review of the study, vaccination information, and illustrations of concepts like randomization.⁸³ From the significant refusal rate (4.5%) and subjects' comments analogizing the study design to African agricultural techniques, scientists concluded that informed consent was possible in developing countries, given reasonable community outreach efforts.⁸⁴ At the same time, subjects continued to have difficulty grasping scientific concepts, even when illiteracy did not impede comprehension.⁸⁵ Investigators also admitted to poor attendance rates at pre-trial education sessions (only 2,607 of 13,555 residents attended at least one of the thirty sessions).⁸⁶

On the other hand, NBAC's community and cultural sensitivity provisions may not substantially change the status quo. First, these recommendations mirror guidelines already pronounced by the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research of Human Subjects.⁸⁷ The International Ethical Guidelines state that investigators must ensure that "the research is responsive to the health needs and the priorities of the community in which it is to be carried out."⁸⁸ Although the guidelines are voluntary, scientific literature over the past decade suggests that U.S. researchers have already recognized the importance of cultural sensitivity and have begun incorporating these elements into their study designs.⁸⁹

Second, these recommendations may not substantially affect practices in the field.⁹⁰ Local medical personnel and volunteers are commissioned to obtain informed consent for U.S. sponsored trials. Their compliance with the study design may not always be practically enforced by U.S. scientists. This problem was discussed in the November 2000 U.S. Embassy's

⁸¹ *Id.* at 50.

⁸² Marie-Pierre Preziosi, Abalye Yam, Malick Neiaye, Aminata Simaga, & Francois Simondon, *Practical Experiences in Obtaining Informed Consent for a Vaccine Trial in Rural Africa*, 336 *NEW ENG. J. MED.* 370, 370 (1997).

⁸³ *Id.*

⁸⁴ *Id.*

⁸⁵ *Id.*

⁸⁶ *Id.* at 370.

⁸⁷ COUNCIL FOR INT'L ORGS. OF MED. SCIS. ("CIOMS") & WHO, *INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS* 25 (1993).

⁸⁸ *Id.*

⁸⁹ See, e.g., Carel B. Ijesselmuiden & Ruth R. Faden, *Research and Informed Consent in Africa—Another Look*, 326 *NEW ENG. J. MED.* 830, 830 (1992).

⁹⁰ Sharon LaFraniere, Mary Pat Flaherty, & Joe Stephens, *The Dilemma: Submit or Suffer; 'Uninformed Consent' Is Rising Ethic of the Drug Test Boom*, *WASH. POST*, Dec. 19, 2000, at A1, available at LEXIS, News Library, WPOST file.

advisory on medical research in China, which stated that while “good practices are widely understood by Chinese researchers, the lack of accountability and poor supervision can mean that good practices are not followed on the front lines of research projects.”⁹¹ A similar situation was documented in Nigeria, in which Pfizer researchers in a 1996 meningitis study used local nurses to confer with families.⁹² The families were only informed about the right to refuse administration of the new drug.⁹³ The researchers neither attempted to translate the full consent form nor informed them that actual medical treatment was available at a “Doctors Without Borders” tent just a few yards away.⁹⁴

Third, even with community outreach and culturally sensitive processes, subjects continue to misconstrue the informed consent disclosures. As pointed out by the study of Presiozi and her colleagues, comprehension of scientific concepts can be difficult, even when illiteracy is not a significant barrier between the research team and the subject.⁹⁵ In addition, some subjects may continue to misunderstand their basic rights as participants, even after being informed of these rights. Researchers in one Bangladesh study found that although most of the 105 enrollees understood the study objectives and attended an informed consent session, forty-eight percent still failed to realize that they could freely withdraw from the study at anytime without penalty.⁹⁶ Furthermore, the requisite amount of effort needed to ensure that *every* subject has a reasonable opportunity to make an informed choice is uncertain. According to one infectious disease specialist in Cape Town, Africa, informing one subject about a study in accordance with U.S. disclosure regulations takes forty-five minutes.⁹⁷ The sessions may take longer when family members or community leaders are also present. This process becomes particularly arduous in large-scale studies enrolling thousands of subjects.

Finally, informed consent does not adequately address the increased potential for abuse induced by the economic, informational, and political power disparity between U.S. investigators and their subjects. The following example illustrates this point.

In 1996, Harvard University and Millennium Pharmaceuticals began a series of genetic studies in conjunction with Chinese collaborators.⁹⁸ The studies were launched one month after China passed a law promoting

⁹¹ John Pomfret & Deborah Nelson, *An Isolated Region's Genetic Mother Lode; Harvard-Led Study Mined DNA Riches; Some Donors Say Promises Were Broken*, WASH. POST, Dec. 20, 2000, at A1, available at LEXIS, News Library, WPOST file.

⁹² Stephens, *supra* note 75, at A1.

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ Preziosi et al., *supra* note 82, at 372. The problem of comprehension extends beyond illiteracy and correlates with a general lack of schooling. *Id.*

⁹⁶ Niels Lynoe, Ziauddin Hyder, Mustague Chowdhury, & Lotta Ekstrom, *Obtaining Informed Consent in Bangladesh*, 344 NEW ENG. J. MED. 460, 460–61 (2001).

⁹⁷ LaFraniere et al., *supra* note 90, at 6.

⁹⁸ Pomfret & Nelson, *supra* note 91, at A1.

sterilization or life-long birth control for individuals with “genetic disease[s] of a serious nature.”⁹⁹

The Harvard/Millennium team aligned themselves with Chinese officials accused of using coercion to increase enrollment in prior studies.¹⁰⁰ In this case, officials organized local cadres to encourage DNA collection on behalf of “thought works” in the rural province of Anhui.¹⁰¹ Historically, locals who refused to participate in “thought works” were penalized with unfavorable taxes, divisions in land, or other subtle and blatant forms of pressure.¹⁰² In Beijing, scientists collected DNA from 1,000 women working at a petrochemical plant for a reproductive study.¹⁰³ In a country governed by a strict population control policy, the women in this study were granted special government permission to become pregnant.¹⁰⁴

The Harvard/Millennium researchers also advertised free health care for study participants. In Toutuo township, health officials and doctors promised villagers free exams, test results, follow-up care, and a “health card” for future discount treatment in exchange for blood samples.¹⁰⁵ Fifteen hundred people arrived, many of whom had not seen a doctor since China’s free health care program collapsed.¹⁰⁶ Wang Mengfeng was one villager who intentionally donated blood to receive treatment for his stomach illness.¹⁰⁷ After submitting to tests, the Harvard/Millennium research team diagnosed him with gastritis and gave him a health card. Unfortunately, because the local clinic failed to receive the promised outside funding from study sponsors, clinicians refused to honor Wang’s health card for treatment.¹⁰⁸ Wang and his wife borrowed money for medical care. When this money ran out, his health deteriorated.¹⁰⁹ Wang died recently at age thirty-four.¹¹⁰

G. INFORMED CONSENT IS NOT ENOUGH

Although there are colorable criticisms aimed at the concept of informed consent, NBAC’s recommendations continue to set commendable standards for researchers to strive to attain. At the same time, further measures must be established in order to reasonably protect subjects in developing countries from objectification and exploitation. Chapter Four of the NBAC report proposes using post-trial obligations as an additional protective measure. The next part of this note defines these recommendations and discusses how NBAC offers to execute them.

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² *Id.*

¹⁰³ *Id.*

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

V. POST-TRIAL INTERVENTIONS

A. NBAC'S PROPOSED POST-TRIAL REQUIREMENTS

NBAC recommendation 4.1 presumptively obligates scientists and sponsors to provide all subjects with “continued access for all participants to needed experimental interventions that have been proven effective for the participants.”¹¹¹ Research proposals submitted to the IRB must describe any pre-research negotiations and explain how successful interventions will become available to some or all of the host population.¹¹² According to NBAC, scientists should ensure that post-trial interventions are in place and inform participants about available interventions.¹¹³ While the financial onus of providing post-trial benefits does not fall squarely on researchers, they are obligated to advocate for post-trial aid with the research sponsors.¹¹⁴ Post-trial aid is not mandated if the investigational treatment is unsuccessful.¹¹⁵ In addition, alternative community benefits suggested by local leaders may be substituted for the proposed continuation of investigational treatments.¹¹⁶

B. JUSTIFICATIONS FOR POST-TRIAL INTERVENTIONS AND CRITIQUES

There are two main justifications for post-trial obligations. First, a fiduciary relationship exists between the scientist and subject.¹¹⁷ Like physician-patient interaction, scientists wield greater power over subjects through greater knowledge and a dynamic of trust. In developing countries, the power imbalance is accentuated by economic, cultural, and political disparities. Moreover, subjects who benefit from treatment during the trial may experience a loss when these treatments are suddenly withdrawn.¹¹⁸ Because subjects in developing countries occupy the vulnerable position in this relationship, NBAC contends that scientists have a responsibility to ensure that subjects continue to benefit even after the study ends. Second, “justice as reciprocity” dictates that subjects who put themselves at risk for a study deserve to be compensated for their sacrifice.¹¹⁹

¹¹¹ NBAC, *supra* note 8, at 74.

¹¹² *Id.* at 65.

¹¹³ *Id.*

¹¹⁴ *Id.* at 64.

¹¹⁵ *Id.* at 74.

¹¹⁶ *Id.*

¹¹⁷ *Id.* at 58. See generally Kara H. Ching, Note, *Indigenous Self-Determination in an Age of Genetic Patenting: Recognizing an Emerging Human Rights Norm*, 66 *FORDHAM L. REV.* 687, 704 (1997).

¹¹⁸ NBAC, *supra* note 8, at 58.

¹¹⁹ *Id.* at 58–59. See also Leah E. Hutt, *Freebies for Subject 641: A Discussion of the Ethical Prospect of Providing Drug Trial Subjects with Post-Trial Access to the Drug Tested—A Canadian Perspective*, 6 *HEALTH L.J.* 169, 183 (1998).

1. *Criticism: The Incompatibility of Fiduciary Responsibilities, Therapeutic Misconception, and Undue Influence*

Several criticisms may be directed at NBAC's justifications for post-trial aid. First, a tension exists between the fiduciary justification and therapeutic misconception. Although scientists have an affirmative duty not to harm their subjects, their primary goal is to conduct studies that benefit others through knowledge. When scientists and research sponsors are analogized to fiduciaries and compelled to extend health care and drug access beyond the scope of the study, this distinction becomes blurred. Upon being informed of these post-trial benefits, it may be difficult for subjects to differentiate between physicians obligated to care for them and scientists now compelled to care for them. In the words of one Johnson and Johnson study participant from Eastern Europe, "I believe they can cure me sooner. I am honored to be chosen for an American experiment."¹²⁰ By imposing post-trial requirements on U.S. sponsored studies, this sentiment may become even more prevalent.

Tension also exists between the "justice as reciprocity" justification and undue influence.¹²¹ Traditional ethical standards hold that researchers should refrain from providing incentives that unduly influence study enrollment.¹²² Supporters of post-trial obligations argue that free health care and drug access are not inducements, but compensation for risk-taking.¹²³ Logic, however, dictates that differentiating between compensation and undue influence may be difficult. To illustrate, one can ask why subjects with life-threatening illnesses in developing countries would walk away from a study with post-trial benefits. Those administered beneficial investigational drugs during the study would be better off. Those who receive placebos or ineffective drugs would arguably be in the same position they would have been in with or without the study. The latter group, however, would later benefit because study sponsors and scientists would be bound to compensate them for their risk. For subjects with little or no health care, this gamble may be too attractive to turn down. Thus, the situation may be defined as an undue influence.

Despite these conflicts, our goals of preventing exploitation and objectification are better accomplished when post-trial interventions are in place. Compelling post-trial interventions levels the financial playing field between U.S. scientists and subjects. If researchers and sponsors are given additional financial obligations, they will less likely conduct trials for drugs that the study population cannot afford. For example, Robert S. Hogg and his colleagues estimated that adopting the current triple combination

¹²⁰ LaFraniere et al., *supra* note 90, at A1.

¹²¹ Hutt, *supra* note 119, at 182–83. See also Neal A. Halsey, Alfred Sommer, Donald A. Henderson, & Robert E Black, *Ethics and International Research: Research Standards Are the Same Throughout the World; Medical Care Is Not*, 315 BRIT. MED. J. 965, 965 (1997). Cf. Kevin M. King, Note, *A Proposal for the Effective International Regulation of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT'L L. 163, 201–03 (1998) (providing a brief discussion on the fiduciary duty relationship).

¹²² See, e.g., CIOMS & WHO, *supra* note 87, at 18; WORLD MED. ASS'N, *supra* note 53, ¶ B23.

¹²³ Hutt, *supra* note 119, at 183.

antiretroviral therapy would cost Malawi, Mozambique, Uganda, and Tanzania more than fifty percent of their GDP.¹²⁴ Hence, testing the antiretroviral cocktail on the host population in these countries might be unethical. In another example, the drug mefloquine was found to be an effective treatment against malaria through clinical tests in Malawi.¹²⁵ Twenty years after this discovery, however, mefloquine is still unavailable to the Malawi people.¹²⁶ Requiring post-trial interventions would either scare off scientists who attempt such studies without regard for their subjects or force them to deliberate more thoughtfully before making the drugs available to the subject population.

Post-trial obligations may also encourage scientists to collaborate with one another so that data is gathered from one subject population in a cost-effective manner. Scientists from different studies may combine their studies so that post-trial interventions need only be provided for one group of subjects. If this idea is not taken to the extreme, it may encourage the efficient use of resources among scientists and sponsors.

2. *Criticism: Diverts Necessary Research Away from Developing Countries*

Other researchers contend that post-trial requirements increase overseas research costs and siphon U.S. sponsored studies away from developing countries.¹²⁷ The Pharmaceutical Manufacturers Association estimated that in 1993 the industry invested approximately \$12.6 billion to produce new conventional drugs.¹²⁸ Additionally, an average of between \$231 and \$359 million is invested in the development of a single drug over a twelve-year period.¹²⁹ Fewer than one of every ten drugs recoups these developmental costs.¹³⁰ If study sponsors are obligated to provide free drug access at the end of the trial, then the increase in cost may curtail their involvement in overseas projects.

The NBAC proposal recognizes this argument, but reiterates the need to conduct studies responsive to the health needs of the subject population. Even with the financial risks involved in the creation of a drug, the General Accounting Office ("GAO") estimates that the pharmaceutical industry was amply rewarded in 1993 with a profit of approximately \$1.2 billion.¹³¹

¹²⁴ Robert S. Hogg, Aslam Anis, Amy E. Weber, Michael V. O'Shaughnessy, & Martin T. Schechter, *Triple Combination Antiretroviral Therapy in Sub-Saharan Africa*, 350 LANCET 1406, 1406 (1997). Cf. Michael Eddleston, Krisantha Weerasuriya & Piero Olliaro, *Ethics Review and Clinical Trials*, 351 LANCET 1065, 1065 (1998) (arguing that study populations should benefit from studies in which they participate).

¹²⁵ NBAC, *supra* note 8, at 62.

¹²⁶ *Id.*

¹²⁷ Parry, *supra* note 23, at 328–29.

¹²⁸ Nina J. Crimm, *A Tax Proposal to Promote Pharmacologic Research, to Encourage Conventional Prescription Drug Innovation and Improvement, and to Reduce Product Liability Claims*, 29 WAKE FOREST L. REV. 1007, 1036 (1994).

¹²⁹ *Id.* at 1018.

¹³⁰ *Id.*

¹³¹ *Id.* at 1036.

Proposed NBAC suggestions for implementing post-trial interventions focus on the concept of “prior agreements.” Prior agreements are “arrangements for making proven interventions available when a successful clinical trial has ended.”¹³² These arrangements may include agreements to provide free or low-cost licenses to local manufacturers who can produce the investigational drug at a cheaper price. Some critics argue that prior agreements for international research can be breached and delay or prevent research in developing countries, in addition to unduly burdening researchers by obligating them beyond the scope of their duties.¹³³ Furthermore, they can be logistically, procedurally, and substantively difficult to implement.¹³⁴ NBAC, however, has not found any of these arguments persuasive.¹³⁵

3. *Criticism: Creates a Double Standard Between Developing Countries and the United States.*

Some researchers argue that a double standard exists when post-trial benefits are required for research in developing countries, but are not required for research in the United States.¹³⁶ The absence of continuing interventions in the United States, however, neither justifies its denial to subjects abroad nor suggests that the same provision should not be considered for U.S. subjects.

C. WHAT KIND OF POST-TRIAL INTERVENTIONS SHOULD BE MADE AVAILABLE?

Post-trial aid can include medical treatments, health counseling and education, and implementation of successful interventions.¹³⁷ For example, VaxGen, a California biotechnology firm, negotiated with the Thai government to test an AIDS vaccine in Thailand.¹³⁸ In return, VaxGen agreed to help Thailand with technology and knowledge transfers and to assist in the production of the vaccine if it proved successful. In a similar example, in 1996, Merck Frosst Canada, Inc. agreed to make the drug crixivan available to Canadian subjects until their own provinces were able to cover the costs. When Merck later conducted a similar crixivan study in Guatemala, however, subjects claimed that they were misled to believe that the rewards of participation included lifetime access to the crixivan-complemented HIV triple cocktail.¹³⁹ Merck insisted that subjects were only guaranteed access to crixivan for five years, with the *possibility* of receiving additional drugs.¹⁴⁰ These Guatemalan subjects now worry that

¹³² NBAC, *supra* note 8, at 66.

¹³³ *Id.* at 67–72.

¹³⁴ *Id.*

¹³⁵ *Id.*

¹³⁶ *Id.* at 71.

¹³⁷ *Id.* at 61–64.

¹³⁸ *Id.* at 66. *See also* Bollag, *supra* note 41, at A41.

¹³⁹ Tessa Tan-Torres Edejer, *North-South Research Partnerships: The Ethics of Carrying Out Research in Developing Countries*, 319 *BRIT. MED. J.* 438 (1999).

¹⁴⁰ *Id.*

the HIV virus will resurface with increased drug resistance when the triple cocktail supply runs out.¹⁴¹

D. MAKING POST-TRIAL BENEFITS A REALITY

NBAC recommendation 4.1 provides:

Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure . . . continued access for all participants to needed experimental interventions that have been proven effective for the participants. . . . [R]esearch protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the research should justify to the ethics review committee why this is the case.¹⁴²

NBAC's post-trial requirements focus on the pre-trial planning and IRB review process. Requiring scientists to prospectively plan their studies is laudable, but regulating the informational content of a study proposal cannot compel the subsequent delivery of post-trial aid. Scientists lack the financial resources and IRBs lack the oversight authority necessary to ensure that post-trial aid becomes available. This endeavor requires the support and participation of study sponsors to be successful.

There are different types of sponsors. "Private for-profit" sponsors possess the capital to finance post-trial aid, but have obligations to shareholders and clients to earn profits. "Philanthropic" sponsors often have limited finances which constrain their ability to continue sponsoring post-trial interventions. Government entities fund studies furthering public health goals, but are accountable to constituents to use public funds wisely.

Because the government is a major sponsor of clinical research, the adoption of NBAC's post-trial recommendations by federal agencies is questionable. These recommendations could either increase federal spending or decrease the number of projects. Both of these outcomes adversely affect the government's interests. In addition, government sponsors may unfairly bear the burden of post-trial aid. Although many studies are initially funded by governmental and charitable institutions, private for-profits ultimately reap the financial benefits of positive study outcomes. The Office of Technology Assessment reports that the government is a major, yet indirect, supporter of pharmaceutical research and development through tax deductions, tax credits, grants to academics, training of scientists, and funding from the NIH, Alcohol, Drug, and Mental Health Administration, and Public Health Service.¹⁴³

E. CREATING FINANCIAL INCENTIVES FOR SPONSORS

Assuming that informed consent does not adequately protect and that post-trial benefits are a desirable complement, it seems odd to rely solely

¹⁴¹ *Id.*

¹⁴² NBAC, *supra* note 8, at 74.

¹⁴³ Crimm, *supra* note 128, at 1037.

upon regulatory schemes when, historically, we have created financial incentives to influence the behavior of our health care industry.

For example, the Orphan Drug Act of 1983 provided drug manufacturers with three incentives to develop treatments for rare disorders or diseases primarily affecting lower income populations.¹⁴⁴ First, the Act provided companies investing in the research and development of “rare diseases”¹⁴⁵ with a fifty percent tax credit based on the cost of clinical trials conducted during the drug approval period.¹⁴⁶ Second, the government agreed to provide additional funding and support to the clinical trial and approval processes of orphan drugs.¹⁴⁷ Third, manufacturers received a guaranteed seven-year period of exclusivity on the drug, even for those not patentable.¹⁴⁸ In 1992, Senators Kassebaum and Metzenbaum proposed to amend the Act so that the seven-year monopoly on an orphan drug would end if the company recouped \$200 million in sales.¹⁴⁹ This bill was defeated and never came before the full vote of the Senate.¹⁵⁰ Opponents of the Orphan Drug Act argue that the pharmaceutical industry received a financial windfall at the expense of American taxpayers.¹⁵¹ In response, proponents of the Act point to the scientific advances and increased enthusiasm to research orphan diseases like cystic fibrosis, Gaucher’s disease, and Huntington’s Disease.¹⁵²

A similar situation developed with the section 936 tax credit, which was legislated to encourage industry development in Puerto Rico.¹⁵³ According to a 1992 GAO report, section 936 saved Johnson and Johnson \$1.117 billion in taxes between 1980 and 1990, SmithKline Beecham saved \$987 million, Abbott Labs saved \$860 million, and Pfizer saved \$759 million.¹⁵⁴ During the same period, the companies charged fifty to sixty percent more for prescription drugs in the United States than in any other industrialized nation.¹⁵⁵ In a Congressional testimony on this report, Senator Pryor argued that the GAO figures demonstrate the extravagant abuse of section 936. In response to this argument, some point out that the tax credit encouraged twenty-two drug manufacturers to build thirty-eight factories in Puerto Rico.¹⁵⁶ They argue that Senator Pryor’s figures are based on “sticker prices” and do not accurately reflect the prices consumers

¹⁴⁴ Patricia C. Kuszler, *Balancing the Barriers: Exploiting and Creating Incentives to Promote Development of New Tuberculosis Treatments*, 71 WASH. L. REV. 919, 954–55 (1996).

¹⁴⁵ According to the Act, a “rare disease” is one that affects less than 200,000 people in the United States. *Id.* at 955.

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

¹⁴⁸ *Id.*

¹⁴⁹ Jonathan L. Mezrich, *International Tax Issues of the U.S. Pharmaceutical Industry*, 10 AKRON TAX J. 127, 164 (1993).

¹⁵⁰ *Id.* at 165.

¹⁵¹ 138 CONG. REC. S6632 (1992) (statement of Sen. Pryor). Genentech recovered ten times its cost of producing a growth hormone for pituitary deficiencies, earning the company \$580 million on the drug alone in its first five years of exclusive marketing. *Id.*

¹⁵² Kuszler, *supra* note 144, at 655. See also Crimm, *supra* note 128, at 1074.

¹⁵³ Mezrich, *supra* note 149, at 151–52.

¹⁵⁴ 138 CONG. REC. S6632, 6334 (1992) (statement of Sen. Pryor).

¹⁵⁵ *Id.* at S6633.

¹⁵⁶ *Id.*

actually pay with discounts and rebates.¹⁵⁷ They also assert that section 936 is needed to ensure that U.S. manufacturers remain competitive in the international drug market. Current U.S. laws prevent companies from taking advantage of tax sparing, a practice generally sanctioned in Europe.¹⁵⁸ Tax sparing occurs when one country allows its own taxpayers to claim a foreign tax credit on a tax not actually paid to another government.¹⁵⁹ Because this practice allows foreign pharmaceuticals to operate in developing countries at a lower cost than U.S. firms, the section 936 credit levels the economic playing field between the United States and their foreign counterparts.¹⁶⁰

As exemplified by the Orphan Drug Act and section 936, the biggest challenge facing the creation of another tax credit for pharmaceuticals is balancing a potential “financial windfall” with the prevention of exploitation in developing countries. On the one hand, another tax credit might detrimentally affect American taxpayers. According to Senator Pryor:

We give drug manufacturers FDA approval for drugs, then a patent from anywhere between 8 to 10 years, which allows them to charge monopoly prices for their drugs. Then we give them millions of dollars in research credits each year to find the cures for the diseases of our time. Then we underwrite the cost of research and development through billions of dollars in federally funded NIH grants. Not satisfied with this, then we turn around and give them hundreds of millions of dollars in tax deductions to market and to advertise their products. To top it all off, Mr. President, then we give them billions of dollars in section 936 tax breaks in Puerto Rico, to go to Puerto Rico and manufacture the drugs we use in America.”¹⁶¹

On the other hand, creating a narrowly tailored tax credit to cover solely the *costs* of ongoing post-trial drug access, education, and basic treatment for subjects would limit the egregiousness of any potential windfalls. Although these savings will be modest, they might still be attractive enough to encourage the financing of post-trial programs. Additionally, the Legislature can create special tax credits for sponsors who transfer technology to developing countries, allowing for the production of successful drugs at lower costs. If legislators fear that companies will abuse the credit, then they can place a maximum dollar limit on the claimed amount.

Alternatively, the Legislature can design a new fast-track FDA approval process. The fast-track program would allow drug companies to sell their drug earlier, thus creating an incentive for them to act ethically. There are currently two types of “fast-track” programs utilized by the FDA. First, the Subpart E provisions initiated in 1988 allow researchers to compress the Phase III trials for life-threatening and seriously debilitating

¹⁵⁷ Mezrich, *supra* note 149, at 133.

¹⁵⁸ *Id.* at 132.

¹⁵⁹ *Id.* at 157.

¹⁶⁰ *Id.*

¹⁶¹ 138 CONG. REC. S6632 (1992) (statement of Sen. Pryor).

diseases.¹⁶² Using the “Subpart E” fast-track decreases the FDA review period by an estimated 3.3 years.¹⁶³ The second fast-track program currently in effect is the 1993 initiated “surrogate marker” program.¹⁶⁴ Under this route, manufacturers can expedite the approval process if the new drug is “effective with respect to a surrogate endpoint that can be reasonably correlated to a clinical benefit for patients suffering from a similar, but not identical, seriously debilitating disease or disorder.”¹⁶⁵

A new fast-track route developed for drugs tested overseas would give priority to applications based on studies conducted in compliance with NBAC’s informed consent regulations. In addition, applicants would be required to prove that appropriate mechanisms are in place to provide post-trial interventions immediately if FDA approval is granted. Research sponsors would provide letters of intent to the FDA and host country, prove that funding has already been set aside, and explain how the interventions will be locally implemented (e.g., letters of intent from local health providers). If the legislature is concerned that the program will be abused, it can limit the scope of the fast-track process or create additional conditions on its use.

VI. CONCLUSION

UNAIDS estimates that in sub-Saharan Africa in the year 2000, there were 25.3 million people living with the HIV/AIDS virus and 2.4 million expected deaths.¹⁶⁶ Subjects in developing countries facing these circumstances lack the resources necessary to keep their illnesses in check and, consequently, often place unequivocal trust in American products. Because U.S. researchers and sponsors wield greater financial, political, and informational power over subjects in developing countries, the potential for exploitation increases.

Historically, the United States has relied on informed consent as protection against exploitation and objectification of its own medical patients and research subjects. The effectiveness of informed consent, however, comes into question when the practice is transposed to foreign contexts. NBAC’s recommendations would prevent exploitation in ideal situations, but implementing them in practice is problematic.

Post-trial requirements can level the financial disparity between U.S. research teams and subjects, ensuring that subjects will not be entirely abandoned when successful interventions are discovered. The success of this idea depends upon sponsors providing the additional costs of post-trial programs. Relying on regulations alone cannot accomplish this goal. The power to effectuate this change lies in the hands of the Legislature and its ability to create financial incentives to fund post-trial interventions. Some

¹⁶² Kuszler, *supra* note 144, at 960.

¹⁶³ *Id.*

¹⁶⁴ *Id.*

¹⁶⁵ *Id.*

¹⁶⁶ *Plan Aims to Prevent Spread of HIV Worldwide*, *supra* note 6.

suggested incentives include tax breaks for studies in compliance with NBAC's recommendations and eligibility to use a FDA fast-track program. While we hope that researchers and study sponsors will act in the best interest of their subjects without prodding from the government, these legislated incentives and NBAC's proposed recommendations will ensure that adequate protection for subjects will exist in most situations.