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Beyond Biases and Barriers: Incorporating Women into International Clinical Research

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The preeminent ethical challenge to international research is the application of principles to biomedical research in a multicultural world, amidst a multiplicity of health-care systems and considerable variations in standards of health-care. Progress in medical care and disease prevention depends upon an understanding of physiological and pathological processes and epidemiological findings, and requires time researching human subjects. Before watershed events of the mid-1900s, international research with human subjects was infrequently carried out by, or strictly supervised by, investigators concerned with establishing informed consent or conducting thorough risk analyses.[1] Ethical protocol was largely nonexistent in regards to the aims and conduct of both international and domestic research, and as a result, clinical participants were frequently ignorant of the nature and degree of even known risks of their participation.[2]

The first international instrument on the ethics of medical research, the Nuremberg Code, was promulgated in 1947 as a consequence of the atrocious experiments on unconsenting prisoners and detainees during the Second World War.[3] The Code, designed to protect the integrity of the research subject, set forth an ethical standard to be applied to research involving human subjects, emphasizing voluntary consent.[4] Similarly, national clinical regulations were inspired by the respective demons of several countries with their own colorful histories of clinical discovery. The United States and the U.K., two of the most active nations conducting and funding international research, shaped clinical regulations in the shadow of public exposures of human rights violations revealed shortly after World War II.[5] (e.g., The Tuskegee Syphilis

[1] Charles R. McCarthy. *Historical Background of Clinical Trials Involving Women and Minorities* 69 ACADEMIC MEDICINE 695, 695-96 (1994) (before the mid-1940s, clinical research was literally unreviewed; researchers could go abroad and escape all forms of regulatory scrutiny as to their methods or clinical development operations;); *See also,* James v. Lavery, *Monitoring and Oversight in Critical Care Research,* 8 CLINICAL CARE 403, 403-405 (explaining that peer review of clinical research could have improved the ethical standards of the early 1900s despite a lack of regulatory overview, an absence which she claims allowed researchers to inject elderly indigent patients with live cancer cells in the early 1960s, and permitted an ethically dubious and unsuccessful chimpanzee-to-human kidney transplant at Tulane University in 1960.)

[2] McCarthy, *supra* note 1, at 696.

[3] *Id*. at 697.

[4] 11 *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law,* 181-82 (1949) [hereinafter, The Nuremberg Code] ("[T]he voluntary consent of the human subject is absolutely essential. This means 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.")

[5] *See, e.g.,* Margaret Liu & Kate Davis, A CLINICAL DRUGS MANUAL FROM THE DUKE CLINICAL RESEARCH INSTITUTE. 320-343 (2nd. ed. 2010). (explaining that the aftermath of the Tuskegee study and the thalidomide tragedy of the 1950s led to the 1962 Kefauver-Harris Amendments in the U.S., which required proof that drugs are

Study [1932–1972], Europe's drug tragedy with thalidomide [1960s], and the Holmesburg Prison testing program [until the early 1980s]).[6] This history of research abuse raised the index of suspicion both among legislatures and amongst those in the research community, including potential participants. Their suspicions created incentives to bar minority research participation and generated a climate of proactive preclusion for formerly abused classes of study participants.

As a result, domestic and international regulations were drafted in such as way as to categorically preclude women from many forms of international clinical study. In the late 1970s, conservative regulations and guidelines issued by the United Kingdom's Department of Health and the United State's Food and Drug Administration (FDA) encouraged the exclusion of women of childbearing age from large-scale clinical trials, conducted both domestically and internationally. For example, FDA guidelines promulgated in 1977 advised that women of "childbearing potential" participate in trials only after Phase II (efficacy and safety) trials and (female) animal reproductive studies have been completed.[7] The U.K adopted an almost identical policy for pregnant and pre-menopausal women.[8] The U.S. and the U.K. were the earliest leading nations funding and organizing international research; therefore, these policies shaped global research models of scientific and ethical practice.[9]

This international protectionist and exclusionary policy proved to be fundamentally disruptive to the progression of women's interests in health research. Because drug trials based clinical findings from results of tests using the male body, a form both physically and physiologically different from that of the female, drug therapies were inadequate for women.[10]

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both safe and effective before marketing them and provided the basis for the current IND (Investigational New Drug application). Drug safety was not the subject of any legislation in the U.K. until after the thalidomide disaster, following which, the Committee on Safety of Drugs was set up in June 1963 by the Health Minister in consultation with the medical and pharmaceutical professions and the pharmaceutical industry. The Medicines Act of 1968 the replaced most of the previous legislation on the control of medicines for both human and veterinary use.)

[6] *See* R.H. Kampmeier. *The Tuskegee Study of Untreated Syphilis*. 65 SOUTH MED J. 1243, 1247–51 (1972) (explaining that in the Tuskegee study, 412 poor African- American men with untreated syphilis were followed and studied even after penicillin, a cure for the disease, became available); *Medicine: The Thalidomide Disaster.* Time. Aug. 19, 1962, at 15 (describing the birth defects arising from thalidomide usage); Allen Hornblum, ACRES OF SKIN: HUMAN EXPERIMENTS AT HOLMESBURG PRISON 310 (1998) (describing the decades-long dermatological, pharmaceutical, and biochemical weapons research projects involving testing on inmates during the Holmesburg Prison testing program.)

[7] Federal Policy for the Protection of Human Subjects. 45 C.F.R. §§ 46.101–124. (1991).

[8] John Griffin, THE TEXTBOOK OF PHARMACEUTICAL MEDICINE. 318 (6th ed. 2009).

[9] M.N. Prout. *Participation of Women in Clinical Trials of Drugs Therapies: a Context for the Controversies*. 3 MED GEN MED 60 (2001).

[10] Vanessa Merton, *The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. Women) from Biomedical Research.*13 AM. J OF LAW & MED. (1993**).** (Robert Levine succinctly laid out the dilemma that confronts women who need medical care: "It is the custom in the United States to develop new drugs based upon

However, once therapies by a predominantly male sample became available in the marketplace, practitioners were free to offer the therapy to women without prior testing.[11] As a result, women across the world were taking drugs without calibration for their specific physiological needs, and suffering from an absence in clinical research.[12]

The protective clinical research, inattentive to injuries, conditions, and diseases that primarily threatened women's lives, rendered physicians utterly ignorant as to how certain drugs affected the female body. The male-centered history of clinical discovery, built around the masculine form and developed primarily by men, led to inadequate therapies. The long-term damage of the approach, however, was its contribution to a systemic form of ethical clinical abuse: the development of a clinical model that failed to incorporate women's experience in clinical trials.

In this paper, I address the human rights issues that arise from the unethical treatment of women in clinical research worldwide. I develop first a background for the discourse, explaining the history of international human rights legislation specific to clinical research. I then explain how women became excluded from international clinical trials, emphasizing the role of the

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testing of their safety and efficacy almost exclusively in adults who are incapable of becoming pregnant. . . . As a consequence, most drugs must contain on their . . . labels a statement to the effect that their safety and/or efficacy have not been established in children and/or pregnant women. In fact, it might be more appropriate to include in such statements that the safety and/or efficacy of the drug has not been established in *women who are capable* of *becoming pregnant.* . . .It is common practice in this country to administer drugs approved for use in non-pregnant adults to pregnant women and children.
Such administration is conducted according to the usual standards of medical practice without rigorous testing of safety and/ or efficacy. In this way we have a tendency to distribute the unknown risks of such activities not randomly but rather capriciously. In addition, we have no assurance that, should the risks materialize as harm, they will be detected."); *Drug Testing on Men Only,* WASH. POST, Dec. 8, 1992, at 214 (quoting Nancy Buc, former General Counsel at Food and Drug Administration, "For many if not most drugs on the market, no one really knows whether they behave any differently in women. Nobody really knows what their role is or should be in pregnancy.")

[11] *See* Robert Walker, *Heart Studies Ignore Women,* CALAGHERY HERALD, Oct. 19, 1991, at B2 (report on presentations at the annual meeting of the Canadian Cardiovascular Association explaining historical administration of cardiomuscular and pulmonary therapies that were unsuited to the female physiology and pharmacology); Caroline Mallan, *MDs Assume Men Need Better Care,* TORONTO STAR, July 26, 1991, at A26 (Canadian men over the age of 45 more than twice as likely as women with similar heart disease to undergo diagnostic angiography and three times as likely to have bypass surgery; doctors don't offer heart surgery to women because they may believe that women don't need to return to work after heart attacks.)

[12] *See,* Jeannette R. Ickovics & Judith Rodin, *Women and AIDS in the United States - Epidemiology, Natural History, and Mediating Mechanisms,* 11 HEALTH PSYCHOL. 110, 112 (1982) (although women represent more than one-third of all cases of AIDS globally and die significantly sooner after diagnosis than men with AIDS, and despite important gender differences in all phases of the disease process, women are still excluded from most biomedical and psychosocial research, and white males predominate in almost all clinical AIDS trials); Gina Kolata, *AIDS Research on Drugs Bypasses Addicts and Women,* N.Y. TIMES, Jan. ***5,*** 1988, at C1, C7 (recounting the heroic, but unsuccessful, efforts of leading epidemiologist Dr. Zena Stein to get funding from NIH and the American Foundation for AIDS Research to study the disease in women.)

regulations guiding the standards employed worldwide by researchers and clinical institutions. Then, I explain how this exclusion began to manifest as human rights abuses as women in clinical research faced challenges of informed consent and access struggles within the clinical model of drug development. Finally, I construct a model for ethical clinical research, building within the framework of leading international human rights doctrines, but incorporating theories used by biologist and human rights scholar H. Beaqueart and bio-ethicist Kaushik Sunder Rajan. In a case study, I apply this "feminist" model of clinical research. I use a renowned, large-scale clinical study to demonstrate that a clinical trail can legally adhere to international research regulations and ethically treat women according to the elements of a feminist model. Using the oral contraceptive research trials in Puerto Rico, conducted by American and English physicians, I demonstrate that international human rights legislation and feminist ethical concerns can operate alongside each other in a framework for a successful research endeavor.

Historical Development of Human Rights in International Clinical Research

Clinical research has become a global enterprise. Investigators and sponsors must deal with multiple legal jurisdictions, with differing laws, regulations and other rules.[13] (The term "law," as used in this paper, includes both laws and regulations.) These rules establish expectations based on each party's locale. As described below, public and non-profit entities also have various legal constraints. These rules limit the flexibility of investigators (i.e., research sites) when negotiating clinical trial agreements (CTAs).

While the first international instrument on the ethics of medical research, the Nuremberg Code, was never officially adopted in its entirety as law by any nation or as ethics by any major medical association, its influence on global human-rights law and medical ethics has been profound.[14] Its basic requirement of informed consent, for example, has been universally accepted and is articulated in international law in Article 7 of the United Nations International Covenant on Civil and Political Rights.[15] Informed consent, with specific reliance on the

[13] Norman M. Goldfarb. *Laws, Regulations, and Clinical Trial Agreements,* Address at the Society of Research Administrators International 2004 Symposium. (2004) (explaining that for years, researchers have encountered different jurisdictions with differing rules. For example, when conducting research among the Member States of the European Union, researchers must follow the EU Clinical Trials Directive. In addition, they must adhere to additional and often more specific requirements on a state level. Spain, for example, requires different forms of consent in terms of minors than Italy does.)

[14] *See* M.A. Grodin. *Legacies of Nuremberg: Medical Ethics and Human Rights.* 73 JAMA 1676:1682-1683 (2003).

[15] The International Covenant on Civil and Political Rights. art. 7. U.N. Doc. A/6316 (Mar. 23, 1976)

Nuremberg Code, is the basis of the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the guidelines promulgated by the World Health Organization and the Council for International Organizations of Medical Sciences.[16] The Code catalyzed a transnational effort to establish an ethical conduct of research involving human subjects, emphasizing informed and voluntary consent to research.[17]

The Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations in 1948.[18] The General Assembly adopted the International Covenant on Civil and Political Rights in 1966 to give the Universal Declaration legal force. Its Article 7 states, ''No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.''[19] The statement hallmarked the dramatic shift in governing rules of clinical work during the early twenty-first century: a sentiment that all research involving human subjects should strive to protect the rights and welfare of all human subjects of scientific experimentation.

In 1964, the World Medical Association brought together physicians, lawyers, ethicists and researchers from global institutes and hospitals to establish recommendations respecting the Covenant's legal principles. It compiled and issued The Declaration of Helsinki, a long and detailed doctrine defining rules for "research combined with clinical care" and "non-therapeutic research" performed internationally.[20] Today, the Declaration of Helsinki reigns as the fundamental international document in the field of humans rights in biomedical research. The Declaration, amended most recently in 2008,[21] sets comprehensive ethical guidelines for physicians engaged in both clinical and nonclinical biomedical research. The Declaration espouses three principles: beneficence, justice, and human dignity,[22] which serve to foundate its

[16] Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. 2002. [herein after, Guidelines]
[17] Anonymous. *World Medical Association Declaration of Helsinki: Ethical principles for Medical Research Involving Human Subjects*. J AM MED ASSOC, 40: 43–45 (2000).
[18] Universal Declaration of Human Rights, G.A. Res. 217 (III) A, U.N. Doc. A/RES/217(III) (Dec. 10, 1948) [hereinafter the Declaration]; Johannes Morsink, THE UNIVERSAL DECLARATION OF HUMAN RIGHTS: ORIGINS, DRAFTING & INTENT 72 (1999).
[19] *supra* note 17.
[20] E. Emanuel & C. Grady. *The 2000 revision of the Declaration of Helsinki: A step forward or more confusion?* LANCET, Sept. 30, 2001, at 149–53.
[21] J.R Williams, *The Declaration of Helsinki and public health*. BULLETIN OF THE WORLD HEALTH ORGANIZATION 2008, at 650-651.
[22] *supra note 18.*

ethical requirements. The Declaration, for example, mandates that research with humans be based on the results from laboratory and animal experimentation, that research protocols should be reviewed by an independent committee prior to initiation, that informed consent from research participants is necessary, that research should be conducted by medically/scientifically qualified individuals, and that the risks of any trial should not exceed benefits to its participants.[23] Another recently added guideline is intended to provide absolute transparency regarding economic incentives involving in research. Paragraph 22, added in 2000, states in part:

> In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail.[24]

It is important to note, however, that the Declaration of Helsinki fails to include provisions necessitating or even recommending inclusion of female subjects, or mandating that research directives attend to gender-specific conditions, or address the differing affects of drugs on different sex or minority bodies. Because the Declaration excluded provisions requiring clinical studies to include females, the Declaration of Helsinki and its progeny set the stage for a series of international guidelines that failed to incorporate an appreciation for feminist concerns in clinical research.

Without encouragement to include females in clinical drug development, international clinical discovery developed around the male form. The three leading nations of drug development, the U.S., U.K., and Japan, performed domestic drug trials with male participants.[25] As my introductory section outlined, clinical research scares of the 1950s and 1960s inspired protectionist legislation in both the U.S. and U.K.[26] Japan similarly concluded that the hormonal fluctuations and reproductive capacity of females rendered them ill-suited for regulated clinical

[23] *Id.* at 651.
[24] World Medical Assembly, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, (18th ed. 2008) [hereinafter the Declaration of Helsinki].
[25] *See, e.g.,* J.T. Fullerton*, Issues in Clinical Trials Management; Women In Clinical Trials 1950–1993: From Exclusion to Equity*. 49 RES NURS; 1, 8–10, 14–6 (1995).
[26] See *infra* notes 7-9;

participation.[27] Legislatures responded to researchers who sought to limit their liability by passing regulations excluding pre-menopausal women from studies, justifying the effort as an attempt to avoid causing harm to as yet unborn children. Complementing these liability concerns, however, was the unfortunate reality that research in all three of these countries was conducted almost exclusively by men. The gender identity of those conducting and funding clinical research directly resulted in a clinical model designed, unintentionally, to accommodate the male experience in clinical research.[28] This kind of bias precluded researchers from choosing to design trials that accounted for women's experience in medicine,[29] or at the administrative level, choosing to fund research accommodating women in research. [30]

Ultimately, the exclusionist model of clinical research went unchallenged for just a few decades. In the 1970s, women began to enter research and medicine.[31] They began to articulate concerns for the discriminatory impact of exclusion of women in medical research, presenting

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[27] Justin McCurry. *Japan Unveils Plan to Boost Clinical Research.* 369 LANCET: 1333, 1336 (2007).

[28] *See* Carol Tavris, THE MISMEASURE OF WOMEN, 96-98 (1992) (explaining that, to this day, in global premier medical schools, students learn the anatomy and physiology of the 70-kilogram man: what his urine output is, what dosages of medication he should get, etc. A study reviewing eighteen leading anatomy texts used in medical schools found that identifiably male bodies and body parts constitute 64% of the illustrations, while female bodies were used only for 11% of the illustrations, except in the chapters on reproductive anatomy; *see also* Kay Weiss, *What Medical Students Learn About Women,* SEIZING OUR BODIES: THE POLITICS OF WOMEN'S HEATH 12-18 (Claudia Dreifus ed., 1978) (from a gynecology text,"[Plredominantly male. . . researchers, policy makers, and practitioners. . . have typically dealt with differences among types of clients by placing everyone, except white middle-aged men, in special population categories. . . . This special population approach provides a way to incorporate data and experience that is inconsistent with general expectations…but reduces the need to examine and revise the fundamental assumptions that define the standard for normal . . . services); *see also* Rebecca Dresser, *Wanted: Single, White Male for Medical Research,* 22 HASTING CET. RP. 24, 28 (Jan.-Feb. 1992) (biomedical researchers define the white male as the normal, representative human being); *see* Ellen Goodman, *A Health-Research Bias.* BOSTON GLOBE. June 21.1990, at 15. (quoting Representative Patricia Schroeder, Congressional leader, "[Ylou fund what you fear. When you have a male-dominated group of researchers, they are more worried about prostate cancer than breast cancer.")

[29] With respect to mental health and developmental research, the picture is much the same. *See, e.g.,* Lindsay Van Gelder, *The Importance of Being Eleven: Carol Gilligan Takes On Adolescence,* MS., July-Aug. 1990, at 77(quoting Carol Gilligin, "[T]he study of adolescence has been the study of males, in reference to the ongoing work of the Harvard University Project on the Psychology of Women and the Development of Girls); *see also* WOMEN AND DRUGS: A NEW ERA OF RESEARCH 489 (Barbara Ray & Monique Braude eds., 1986) ("The history of drug abuse research shares with other sciences a relative paucity of knowledge about females in particular and about gender effects in general. This bias in knowledge stems from the tradition of using male subjects for animal and human experiments and an unexamined assumption that gender is not an important experimental variable.")

[30] *See* Scott Greenberger, *Science Friction: The Struggle of Female Researchers at NIH,* WASH. POST, July 11,1993, at C3. (An internal task force convened in 1991 to assess the career development and status of women scientists at NIH. It found that women made up only 18% of the tenured scientists, although they constituted 30% of the last decade's post-docs (the traditional track to senior status). Extensive reports by female scientists of anti-woman bias at NIH range from denial of lab time, and rejection of domestic and international project proposals. In 1992, a Washington, D.C. television station ran a six-part investigative report that featured dozens of female NIH researchers alleging discriminatory treatment)

[31] *See* Bernadine Healy, *Women in Science: from Panes to Ceiling,* SCIENCE 67 (1992). (Female first-year medical school enrollment steadily grew after the 1960s, from **4%** in 1930, to 9% in 1969, to over 50% in 1990.)

evidence the inclusion of women in clinical discovery was necessary to obtain important information about the efficacy of new drugs and interventions in both sexes.[32] In 1986, the United State's National Institute of Health adopted a policy recommending the inclusion of women in clinical research. Responding to the recommendations of physician associations and the lobbying of women's groups, Congress adopted the NIH Revitalization Act, which required adequate numbers of women for valid analyses of differences related to phase 3 trials.[33] The Food and Drug Administration (FDA) guidelines ended the restriction on women of child-bearing potential in the early 1990s.[34]

This shift in regulatory approach manifested on the international stage soon thereafter. In the 1980s, Europe, Japan and the United States initiated an attempt to harmonize international guidelines with their differing, respective national regulatory requirements, looking to the ethical principles of the Declaration and the International Ethical Guidelines as a baseline.[35] At the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, specific plans for action between these three leading research nations began to materialize, and in April 1990, representatives of the regulatory agencies and industry associations of Europe, Japan and the US met to etch out a common legal framework for conducting clinical trials within their borders and regulating research in other countries. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) produced the first ICH Terms of Reference in 1990. Today, the ICH operates to achieve harmonisation among Europe, Japan and the US to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.[36]

The ICH Guidelines were the first international standards to address the legal and ethical approach to inclusion of women in clinical research. The Guidelines addressed the dangers of drug therapies solely developed with the use of male subjects.[37] ICH Guideline E8, for example, requires that a study population be representative of the target patient population, and specifically mandates that Phase I pharmacokinetic information in women be submitted for

[32] See *infra* note 26, 27.
[33] M.N. Prout. *Participation of women in clinical trials of drugs therapies: a context for the controversies*. 3 MED GEN MED 60 (2001).
[34] Id.
[35] *See supra,* note 5.
[36] Introductory comments to the ICH 20th Anniversary Publication. Found at http://www.ich.org/home.html.
[37] Maria Teresa Ruiz Cantero & Maria Angeles Pardo. *European Medicines Agency policies for clinical trials leave women unprotected.* J EPIDEMIOL COMMUNITY HEALTH. 60 911: 911–913 (2006).

regulatory approval.[38] It further requires dose response data from relevant sub-populations, including categories according to gender. Guidelines E3 and M4E call for a characterization of the patient population, as well as analyses and critical assessment of the data with respect to sex.[39]

Together, the Declaration of Helsinki and the ICH Guidelines stood as the most influential international doctrines defining rules for international clinical research. The ICH Guidelines, of course, were unfortunately only binding upon the U.S., U.K., and Japan. To supply guidelines and regulations for those countries non-party to the ICH, but participants in international research, the World Health Organization and the United Nations Educational, Scientific and Cultural and Organization (UNESCO) founded The Council for International Organizations of Medical Sciences (CIOMS) to prepare the International Ethical Guidelines for Biomedical Research Involving Human Subjects.[40]

In the early 1980s, CIOMS began to compose a set of guidelines which could serve to guide the application of the ethical principles set forth in the Declaration of Helsinki in the construction and conduct of biomedical research; they were developed with particular concern for their application in developing countries, given the socioeconomic circumstances, laws and regulations, and executive and administrative arrangements in those nations.[41] The outcome of the CIOMS/WHO undertaking was the Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects.[42] The Ethical Guidelines used the principles outlined in the Declaration of Helsinki, those of beneficence, justice, and human dignity, to establish a set of rules and recommendations for international clinical research. The Guidelines hold,

> [t]hese three principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of

[38] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Guidelines*. November 19, 2005. (Available online at http://www.ich.org/cache/compo/1.html (accessed April 21, 2011).
[39] *Id.*
[40] Goldfrab, *supra* note 13.
[41] Temple R. *Impact of the Declaration of Helsinki on Medical Research from a Regulatory Perspective.* Address to the Scientific Session, World Medical Association General Assembly, September 2003.
[42] World Health Organization (WHO) Council for International Organization of Medical Services (CIOMS) *International Guidelines for Biomedical Research involving Human Subjects.* Introductory Comments. Nov. 13, 1982. [hereinafter Ethical Guidelines]

> action. The present guidelines are directed at the application of these principles to research involving human subjects.[43]

The recommendations the CIOMS Ethical Guidelines lack an international body or mechanism serving as an enforcement apparatus. However, domestic governments, along with public and nonprofit entities, have developed legal and fiscal methods to bind clinical trial operations to the rules of clinical ethics set forth by international doctrines. Countries with leading research institutions and large government research programs have incorporated these doctrines into their domestic regulations, for trials conducted both within their borders and internationally with government funding.[44]

The Council of Europe, with 44 Member States, developed a Protocol on Biomedical Research which mandates that physicians and researchers operating within the European Union adhere to CIOMS's Ethical Guidelines.[45] It further includes an enumerated Convention on Human Rights and Biomedicine.[46] The Convention inspired the European Clinical Trial Directive in 2001, a doctrine adopting the spirit of the principles and provisions of the Declaration of Helsinki.[47] This became binding on member states in 2004.[48] It, too, made certain clinical practices of the Ethical Guidelines mandatory for all clinical drug trials performed by member states of the European Union.[49]

The United States enforces international guidelines through recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, established by the National Research Act.[50] The Commission issued a report in 1979 (the Belmont Report) that serves as the basis for regulating all research, domestic and

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[43] Ethical Guidelines, *supra* note 42 at 12.
[44] E.J. Cassell. *The principles of the Belmont report revisited. How have respect for persons, beneficence and justice been applied to clinical medicine?* 30 HASTINGS CENT REP 12, 12–21. (2000).
[45] Directive 1998/44/EC of the European Parliament and of the Council of Europe. (August 13, 1998).
[46] *Id.*
[47] European Parliament: Council on the Good Clinical Practice in the Conduct of Clinical Trials. Clinical Trials Directive, 2001/20/EC, April 4, 2001. With the Clinical Trials Directive, the European Union (EU) established a harmonisation of research ethics committees (RECs) across Europe, including the reporting requirements, requirements specific to the time taken to assess a trial proposal and the kinds of issues a committee should take into account.
48 Directive 2001/20/EC of the European Parliament and of the Council of Europe (April 4, 2001).
[49] *Id.*
[50] Office for Protection from Research Risks, National Institutes of Health. *Protecting Human Research Subjects: Institutional Review Board Guidebook.* (1993).

international, sponsored by the federal government.[51] The Report directly adopted the principles articulated in the Declaration of Helsinki,[52] espousing beneficence, justice, and human dignity. It provides a framework stemming from these principles to guide the resolution of ethical problems arising from research involving human subjects.[53] In 1981, the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report. The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards), and DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects).[54] These regulations beget further regulations promulgated in the spirit of the principles of beneficence, justice, and human dignity.[55]

In Japan, international clinical trials are strictly regulated by the Pharmaceutical Affairs Law and by the Ministry of Health, Labor and Welfare (MHLW) Ordinance on GCP, which was adopted in Japan in 1997.[56] The Ordinance is based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Guidelines.[57] The MHLW provides Ethical Guidelines for Clinical Studies, mimicking

[51] Department of Health, Education, and Welfare. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH. *Belmont Report: Ethical principles and Guidelines for the Protection of human subjects of Research.* Washington (DC): May 20,1978 [herein after the Belmont Report]

[52] The Belmont Report, *supra* note 39. (The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.)

[53] *Id.*

[54] The Food and Drug Administration. 21 C.F.R. **5** 10.90(b) (1993) (research conducted in good faith pursuant to *Guidelines* will be accepted by FDA for review). *See also* 21 C.F.R. **8** 312.145 (1993) ("A person may rely upon the Guidelines with assurance that it is acceptable to FDA.")

[55] In 1991, the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other Departments and Agencies that conduct or fund research involving human subjects as the Federal Policy for the Protection of Human Subjects, or "Common Rule." In 1991, the Department of Veterans Affairs promulgated this same rule at 38 CFR Part 16. Today, the 1991 Federal Policy is shared by 17 Departments and Agencies, representing most, but not all, of the federal Departments and Agencies sponsoring human-subjects research.

[56] H. Yanagawa, S. Abe. *Clinical trials for drug approval: a pilot study of the view of doctors at Tokushima University Hospital*. 53 J MED INVEST. 290, 292–296 (2006).

[57] J. McCurry. *Japan Unveils 5-year Plan to Boost Clinical Research.* LANCET. 129, 133-136 (2007). (For example, Japan's MHLW adopts the Ethical Guideline 13 directly, requiring that informed consent in international clinical work be obtained according to the legal requirements and cultural standards of the community in which the intervention is carried out. Within one week the physician must report to the ethical review committee the details of the case and the action taken, and an independent health-care professional must confirm in writing to the ethical review committee the treating physician's judgment that the use of the investigational intervention was justified according to the three specified criteria.)

the guidelines of CIOMS, and establishes a set of ethical recommendations based on the principles of beneficence, justice, and human dignity.[58]

In addition to domestic regulations, grant institutions and funding bodies have developed fiscal incentives to render the Ethical Guidelines de facto binding upon international research projects. Several of the most prestigious international and multinational organizations funding modern research work have issued ethical guidelines for clinical trials that adopt directly or mimic the Declaration of Helsinki's standards.[59] These funding bodies require all funded projects to abide by enumerated rules of ethics.[60] These incentives work in tandem with those of domestic regulatory bodies to create de facto as well as actual enforcement mechanisms for international ethical guidelines.[61]

The United Nations has led an effort that tracks and analyzes the effects of such regulatory and recommended guidelines on women's experience in clinical discovery. In 1995, the United Nations convened the Fourth World Conference on Women in Beijing, China.[62] Delegates from the UN's Member Nations prepared a Platform for Action;[63] in the enumerations of the Platform, the Conference signaled a clear commitment to the progress of international norms and standards of equality between men and women, proclaiming that the "human rights of women and girl-children are an integral part of universal human rights and must underlie all action."[64] The Platform proceeded to outline a series of recommended actions to ameliorate gender parity; importantly, four of its recommendations specifically address women's experience in health and heath research.[65] Since 1995, the Conference has convened in five-year increments

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[58] *Id.*

[59] Griffin, *supra* note 9, at 430-433. (The U.N., one of the largest sources of funding for AIDS and infectious disease research worldwide, cannot enforce the guidelines legally, but requires their funded projects to abide the rules of the Declaration of Helsinki. Similarly, the World Health Organization requires their projects to abide by their established Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products, and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) requires their grantees to follow the Guideline on Good Clinical Practice, which serve to ensure that data generated from clinical trials are mutually acceptable to regulatory authorities in the European Union, Japan and the United States of America. If countries refuse to follow or neglect certain provisions of these doctrines, funding bodies can revoke funding and disqualify organization or individual from subsequent consideration for research funding.)

[60] See *supra* note 9, at 415.

[61] Scot A. Fritzen. 83 *Reorienting Health Ministry Roles: Capacity and Strategy Gaps.* 83 HEALTH POLICY 73, 75 (2007).

[62] Report of the Fourth World Conference for Women: Beijing Declaration and Platform for Action. U.N. Doc. A/CONF.177/20/Rev.1. Sept. 15, 1995.

[63] *Id.*

[64] *Id.* at 12.

[65] *Id.* at 27-29. ("Provide financial and institutional support for research on safe, effective, affordable and acceptable methods and technologies for the reproductive and sexual health of women and men, including more safe, effective,

to assess international progression in relation to their recommendations; to date, UN Member States have provided three assessments of progress made.[66] In 2000, 2005, and 2010, members of the Conference have reconvened to identify and analyze the remaining gaps and challenges in the implementation of the Platform for Action.[67] Each convention year, regional commissions compose data for presentment, which provides the basis for analysis of trends and challenges in implementation of the Platform's goals. Assessments of the Conference indicate that while the significant players on the global research stage have adopted legislation and funding protocols incentivizing adherence to specified ethical standards in research, regulatory bodies sometimes fall short of enforcing the regulations, or providing national standards for data and research results which appreciate women's interests.[68] Therefore, those performing research in certain

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affordable and acceptable methods for the regulation of fertility, including natural family planning for both sexes, methods to protect against HIV/AIDS and other sexually transmitted diseases and simple and inexpensive methods of diagnosing such diseases, among others; this research needs to be guided at all stages by users and from the perspective of gender, particularly the perspective of women, and should be carried out in strict conformity with internationally accepted legal, ethical, medical and scientific standards for biomedical research; a. Develop mechanisms to evaluate and disseminate available data and research findings to researchers, policy makers, health professionals and women's groups, among others; b. Monitor human genome and related genetic research from the perspective of women's health and disseminate information and results of studies conducted in accordance with accepted ethical standards.")

[66] *See,* Five Year Review of the Beijing Conference at a Special Session of the UN General Assembly (Beijing +5), Ten Year Review (Beijing +10)l Fifteen Year Review (Bejing+15) found online at http://www.un.org/womenwatch/confer/beijing/reports.

[67] In addition to Member States and regional reports, the Conference draws upon a variety of sources of information and statistics to develop its findings, including reports submitted by States parties under the Convention on the Elimination of All Forms of Discrimination against Women; information generated in the context of the Commission on the Status of Women; regional action plans and national reports to regional bodies; as well as and the outcomes of expert group meetings and other activities at regional level. Other sources of information include Common Country Assessments and the United Nations Development Assistance Frameworks, (CCA/UNDAFs), Poverty Reduction Strategy Papers, (PRSPs), national Human Development Reports and national Millennium Development Goal (MDG) reports. (*See supra* note 61 at 2-3).

[68] *See, e.g. Report of the Economic and Social Commission of Asian and the Pacific,* November 18, 2009, found online at http://www.un.org/womenwatch/daw/beijing15/regional_review.html . (The UN's progression analysis shows improvement in some areas, but certain regulatory bodies need to improve in the Asian/Pacific region. During the twenty-third special session of the General Assembly in 2000, for example, the Conference's Beijing +5 meeting presented the findings by five of the United Nations regional commissions (ECAP, ECE, ECLAC, ESCAP, ESCWA). The Economic Commission of Asia and the Pacific (ECAP) conceded in its report that efforts to obtain proper and accurate baseline data on the range of women's health needs was stifled by the lack of reported research trials, and blamed the regulatory bodies in Asian-Pacific countries for failing to enforce reporting rules. *Id.* at 2-4. Moreover, the report held that several governments were failing to develop reliable and valid indicators of women's health status. *Id.* at 5. Thailand's government, for example, continued to rely on contraceptive prevalence rates, life expectancy of women and maternal mortality rates (when available) as sufficient health impact indicators to assess women's health needs. *Id.* Data available for South Korea, then, was comprised of primarily national data reflecting national averages. *Id* at 14.The report acknowledged that it was difficult to obtain data which was already analyzed and presented by age, geographical location (rural, urban), class/income, religion/culture, indigenous and ethnic groups because research projects did not report many required descriptions of the participants in their trials. The lack of broadly available and reliable data made it difficult to develop an-depth approach to improving women's health on a regional level. For example, the Commission could not address targeted questions like which women were

regions still are not properly incentivized to follow international ethical regulatory guidelines. The progressive conclusions have ultimately demonstrated that regulatory and fiscal mechanisms play an important and growing role in improving the feminist experience in research, but many national regulatory bodes must not only *adopt* international ethical standards, but also, strive to *enforce* regulatory measures in order to property incentivize adherence to doctrines like the International Ethical Guidelines.

International efforts to improve women's clinical experience provides true opportunities to effect change in the contemporary research model if they are endorsed by regulatory clinical bodies. Since the turn of the millennium, international regulations have begun to shift away from protectionist policies. While maintaining adherence to the principles of beneficence, justice, and human dignity, for example, the ICH Guidelines and CIOMS's International Ethical Guidelines for Biomedical Research Involving Human Subjects have catalyzed a gender-inclusionary approach to clinical discovery.[69] One of the most significant additions to the International Ethical Guidelines for Biomedical Research Involving Human Subjects occurred in 2006. CIOMS issued a newly-amended Guideline 16, specifically addressing the inclusion of women in international research efforts.[70]

Guideline 16 openly acknowledges that the former policy of excluding women from clinical trials was unjust in that it "deprives women as a class of persons of the benefits of the new knowledge derived from the trials."[71] It holds that such preclusion is an affront to their right of self-determination.[72] The Guideline cautions that although women of child-bearing age should be given the opportunity to participate in research, they should be helped to understand that the research could include risks to the fetus if they become pregnant during the research.[73] The Guideline acknowledges that women in clinical research face unique societal and cultural pressures complementing participation in trials.[74]

However, while facially espousing feminist clinical principle leading international guidelines fail to present advice as to how practitioners or researchers may incorporate gendered

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more at risk for acquiring cervical cancer and less likely to seek screening or treatment in many Asian countries, or which women are dying in pregnancy and childbirth, according to race, region, or age.)

[69] See *supra* note 33, CIOMS Ethical Guidelines, at 3-5.

[70] *Id.*

[71] *Id.* at Commentary on Guideline 15.

[72] *Id.*

[73] *Id.* at 50-51.

[74] *Id.*

concerns into their procedures. Importantly, they lack advice as to how to acquire a feminist form of feminist informed consent in the process of conducting a clinical study on women. Moreover, these guidelines still lack attention to the question as to how rights of trial participants extend after their participation in a clinical effort. Currently, no international legislation requires that trial participants who dedicate their time and energies to drug discovery have access to the drugs after their personal trial participation ceases. In this next section, I explain how attention to these kinds of concerns can and should complement an ethical clinical trial that recognizes the human rights of women clinical participants.

A Feminist Model of Clinical Research

Despite the ethical advances made in the past quarter century, past protectionist policies of law-makers and gender biases and liability considerations of the medical community have lingering effects, both in the design and regulation of contemporary clinical design. To this day, ethical considerations can still fall to the wayside in light of competing economic or efficiency interests.[75] Though regulatory bodies in large nations have adopted and enforced international ethical guidelines, these institutions sometimes waiver in the face of countervailing market forces. In 2008, for example, the FDA announced that it was going to enforce the 1989 version, rather than the later, amended, versions, of the Declaration of Helsinki. [76] The change authorized pharmaceutical operations to run international clinical trials in which patients in the control group (i.e. those who are not getting the experimental drug) could be treated with placebos instead of the best standard medical care.[77] The change has had important practical implications,

[75] Lionel D. Edwards, DESIGN AND CONDUCT OF RESEARCH IN WOMEN: TO INCLUDE OR EXCLUDE: A PHARMACEUTICAL INDUSTRY PHYSICIAN'S PERSPECTIVE 113-14 (1994) (In a confidential 1991 survey of 33 major pharmaceutical houses, conducted by the Pharmaceutical Manufacturers Association, 79% reported that FDA reviewers had required them to exclude women of child-bearing potential from their protocols.)

[76] Dept. of Health and Human Services Food and Drug Administration. *Human Subject Protection Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application.* 21 CFR 312. (2008) Published April 18, 2008, effective October 27 2008.

[77] See *supra* note 9, the Declaration of Helsinki, at paragraph 2a (states specific concepts with regard to the use of a control group: the benefits, risks, burdens, and effectiveness of the new methods should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo or no treatment in studies where no proven prophylactic, or therapeutic methods exist. In a Note of Clarification on paragraph 29, *id,* added in 2002, the Declaration notes, "extreme care must be taken in making use of a placebo control trial and that, in general, this methodology should only be used in the absence of existing proven therapy. However, a placebo controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: (a) where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method; (b) where a

considering that over a third of annual new drug applications the FDA reviews are the product of medical research performed overseas by for-profit Clinical Research Organizations (CROs).[78] Modern reality thus begs the question: can a modern clinical study be both legal, ethical and feminist at the same time? Can science feasibly aim to conduct clinical studies that respect the human rights of their female patients in light of competing market interests? What would patient and scientist participation look like in such a model? In this section and in the following case study, I explore these questions.

Building from the central principles of the Declaration of Helsinki, [79] I propose that clinical research is "ethical" if it employs the principles of beneficence, justice, and human dignity while functioning with an understanding of the need to incorporate women's specific interests in medicine. This model will facilitate a woman's ability to make informed choices, exercise autonomy, and access the standard of care in medicine. This is an approach consistent with much of the commentary following Guideline 16 of the International Ethical Guidelines for Biomedical Research,[80] but slightly improved. Guideline 16 categorically excludes pregnant or nursing women from trials unless the research carries no more than minimal risk for the fetus or infant.[81] In the face of a trial objective to acquire new knowledge about pregnancy or lactation, however, women who are not pregnant or nursing would not be suitable subjects. This Guideline utterly ignores the right of pregnant or nursing women to make their own informed, personal risk-benefit calculus, while imposing no such restrictions on fertile and reproductively active male subjects. My clinical model utilizes a feminist, rather than a protectionist, approach to

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prophylactic, diagnostic or therapeutic method is being investigated for a minor condition in the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.")

[78] *See supra* note 53, at part 312 ("The Food and Drug Administration (FDA) of the United States has ruled that clinical trials performed outside the US no longer have to conform to the Declaration of Helsinki if used to support applications for registration of products in the US. Instead, the International Conference on Harmonization Good Clinical Practice (GCP) has been designated as the new regulatory standard"); *See also* Normile D. Ethics. *Clinical trials guidelines at odds with US policy*. 322 SCIENCE 516 (2008). ("This suggestion met considerable opposition from scientists, ethicists, and consumer groups before and during the consultations. The FDA's justifications included the arguments that it was merely harmonizing its regulations with a global standard, and that legal instruments, such as the US Code of Federal Regulations, cannot embed external documents subject to change beyond the agency's control.").

[79] The Helsinki Declaration, *supra* note 19. (The Declaration proclaims, "Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.")

[80] See *infra*, notes 45-48.

[81] *Id.*

informed consent and participation. Using the insights of biologist and bio-ethicist Helen Beaquert, and human rights scholar K. Rajan, I apply a feminist lens to the interpretation and application of beneficence, justice, and human dignity to propose a model for an inclusionary, feminist clinical model.

The principle of beneficence (i.e.,"do not harm") dictates that all research participants be protected from the foreseeable risks (e.g., physical, psychological, social, or economic) involved in participating in the study of an untested or unproved therapy.[82] Participants in a research study cannot be exposed to situations for which they have not been prepared or otherwise subjected to exploitation.[83] Similarly, the principle of beneficence holds that women cannot be confined to drug therapies which may do them harm without information as to the extent or nature of these harms.[84] Ultimately, the concept provides that the women of society should be protected from a loss of information that could only be gained by the participation of women in studies relevant to their safety and well-being. To protect from flawed or insufficient medical information, women should be incorporated proportionally into research trials, and should not be mandated to rely on solely male-representative medical findings. This includes trials of pregnable, pre-menopausal, lactating, and even pregnant, women[85].

Analyzing recent trends in international research, clinical trials often fail to incorporate the principle of beneficence in such a way, and neglect the significant of gender-balanced information to women's health. A study funded in 2007 by the American Heart Association revealed that in 156 randomized clinical trials performed over the three past decades by the United States, the U.K., Japan, Canada, Australia, and New Zealand, women's participation has been markedly lower than that of males. Until the late 1980s, only 9 percent of clinical participants in these trials, concentrated on issues of heart and lung disease, were women. By

[82] The Belmont Report, *supra* note 39; *See also*, J. Fullerton, *Ethical Considerations Related to the Inclusion of Women in Clinical Trials*, 49 J MIDWIFERY & WOMEN'S HEALTH, 194, 201–202 (2004).
[83] *Id.* at 196.
[84] *Id.* at 197.
[85] *See,e.g.* Dept. of Health Education and Welfare. *National Commission for the Protection of Humans Subjects in Biomedical and Behavioral Research*. Pub. No. 76-127: RESEARCH OF THE FETUS. 65 (1975) ("Therapeutic research directed toward the pregnant woman may expose the fetus to risk for the benefit of another subject and thus is at first glance more problematic. Recognizing the woman's priority regarding her own health care, however, the Commission concludes that such research is ethically acceptable provided that the woman has been fully informed of the possible impact on the fetus and that other general requirements have been met. Protection for the fetus is further provided by requiring that research put the fetus at minimum risk consistent with the provision of health care for the woman. Moreover, therapeutic research directed toward the pregnant woman frequently benefits the fetus, though it need not necessarily do so. In view of the woman's right to privacy regarding her own health care, the Commission concludes that the informed consent of the woman is both necessary and sufficient.")

2006, about a third of clinical trials participants were female, but in secondary prevention trials, females were only participating at a rate of 24.6 percent. Female enrollment was comparable in government/foundation-funded versus industry-funded trials (31.9% versus 31.5%), but the representation of women was consistently low for trials involving heart failure (29%), coronary artery disease (25%), and hyperlipidemia (28%). By contrast, women account for 53% of all individuals with hypertension, 50% with diabetes, 51% with heart failure, 49% with hyperlipidemia, and 46% with coronary artery disease in the world.[86]

The study demonstrates that while enrollment of women in internationally conducted clinical trials has increased in recent decades, women's participation remains low relative to their overall representation in disease populations. More efforts are needed to reach a level of representation that is adequate to ensure evidence-based, sex-specific recommendations. Women must receive health care information at the same level and depth of their male counterparts, in each condition and stage of their reproductive lives, so as to not suffer from the absence of gender-specific information.

The principle of justice includes the rights to equal access, full information, privacy, and respect for cultural and other forms of diversity. In the context of a feminist model of clinical research, this principle would require that everyone in society have equal opportunity to share in the benefits of newly emerging therapies. This principle acts along with the tenets of beneficence to dictate that society is served best when sufficient information is available about both sexes. Additionally, however, the principle of justice serves as the foundation for arguably the most fundamental concept embraced by major international doctrines concerned with drug discovery today: informed consent.

Informed consent is meant to guarantee the voluntary nature of participation in research studies. Because clinical trial agreements are legal documents, much of their content necessarily has a legal flavor to it. The medical community once treated a patient's informed consent to be something like a contract at the beginning of a trial, something to be read and discussed, and then completed with a signature. [87] In a feminist, ethical model of clinical discovery, however, informed consent should develop a more sophisticated meaning. Explained by biologist and human rights scholar Helen Beaquert, a feminist construction of informed consent should

[86] Chiara Melloni, *Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention.* 3 CARDIO OUTCOMES 135, 135-142 (2009).
[87] T.L. Beauchamp, CONTEMPORARY ISSUES IN BIOETHICS. 98 (2nd ed. 1982.)

manifest as an ethical state of a study rather then a static commencement agreement signed into a legal contract.[88] A full consent on behalf of a volunteer comes as she learns and processes the key facts about a clinical trial; she is explained the terms, commitments, benefits and dangers in a straightforward way, in a language accessible for her understanding.[89] [90]

This form of consent gives a volunteer deliberation time before deciding whether or not to participate, and then once committed, promises that the providers of a contract will ensure that a woman's body is provided for and never denied known preventative or successful curative therapies. This form of consent implies full knowledge and a clinician's commitment to caring for a woman while under study, requiring all tests that inform clinicians of known potential dangers of a drug are performed. This type of full, informed contract of consent dictates that a clinician is ready to provide information for subjects at their request, or when trial conditions change, throughout a trial.

Unfortunately, international clinical trials today often wield a less sophisticated understanding of informed consent. In 1991, for example, a team of independent research ethicists in Sweden performed an unannounced series of follow-up studies on clinical trials performed in that country over the prior three years. They meant to determine whether the participants in Sweden's clinical trials had received adequate information about the trial according to the guidelines of the Declaration of Helsinki. Among the studies they reviewed, they targeted one sex-specific gynecological study for an investigation as to the quality of information given to its female participants. Of the 68 patients in the study, 43 women volunteered to participate in its follow-up review. The ethics committee determined that although the patients should have been consulted both orally and in writing when approached and when consent was sought, half the participants had received only oral information to establish their

[88] Helen Bequaert Holmes. *Rights over One's Own Body: A Woman-Affirming Health Care Policy*, 3 HUMAN RIGHTS QUARTERLY, 74, 71-87 (1981).
[89] *Id.* at 76
[90] This is particularly important for women in developing countries. *See, e.g.,* CIOMS: Commentaries on Informed Consent, Guideline 4, *supra* note 33 at 16. (In some populations the use of a number of local languages may complicate the communication of information to potential subjects and the ability of an investigator to ensure that they truly understand it. Many people in extra-Western cultures are unfamiliar with, or do not readily understand, scientific concepts such as those of placebo or randomization. To appreciate this disparate understanding, CIOMS International Ethical Guidelines requires sponsors and investigators to develop culturally appropriate ways to communicate information that is necessary for adherence to the standard required in the informed consent process. The Guidelines further recommend that they should describe and justify in the research protocol the procedure they plan to use in communicating information to subjects. For collaborative research in developing countries the research project should, if necessary, include the provision of resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.)

informed consent for the purposes of the trial. Only 35 women answered that they remembered giving consent; others could not remember, or stated they had not consented. One woman revealed that she had never received any information and that she had been unaware of her participation in a research project until she received the ethicists' follow-up questionnaire. At least 17 out of 43 women had not been aware that they could change their mind about participation, and, even more seriously, 15 out of 43 had not been aware that one of their two operations had been performed purely for scientific reasons. They had never received the written information, prepared by the trial's directors, that the second look operation was of no medical advantage to them, and they were not informed orally. So, 15 women were motivated in their decision to participate by the possibility of receiving treatment, and participated under a deluded perception that the second operation was helping them.[91]

In contrast to such evidence of discrepancies in past clinical discovery, a feminist model of clinical ethics would require that participants receive adequate information concerning the project's aims, methods, expected benefits, and potential hazards and discomforts, at its commencement, and then, at each stage in its progression.[92] Furthermore, experimental subjects should be informed that they can abstain from participation in the study and are free to withdraw their participation at any time, without any risk with regard to the quality of the ordinary treatment.[93] Provided that the participant understands the importance of the information and is fully capable of making a decision, informed consent can be obtained.

In research involving women of reproductive age, whether pregnant or non-pregnant, a feminist model would require only the informed consent of the woman herself. However, in respecting the cultural nuances of transnational clinical trials, the model would hold that if women wish to consult with their husbands or partners or seek voluntarily to obtain their permission before deciding to enroll in research, that is not only ethically permissible but in some contexts highly desirable.[94] Finally, a feminist consent discussion should include information about the alternatives of voluntarily withdrawing from the study, and requires that consent discussions be consistent throughout the course of a study.[95]

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[91] Niels Lynoe, Mikael Sandlund, & Lars Jacobsson, *Informed consent: Study of Quality of Information Given to Participants in a Clinical trial.* 303 BMJ 14, 18 (1991).
[92] See *supra* note 33, CIOMS Ethical Guidelines, at 48.
[93] *Id.* at 50
[94] *Id.* at 49-50.
[95] *Id.*

The final principle underscoring a feminist, clinical effort is that of respect for human dignity. This incorporates the concepts of the right to self-determination and autonomy, and appreciates a component of access.[96] This principle requires due diligence on behalf of clinical researchers to avoid implicit or explicit attempts to coerce a woman to participate in a study. Coercion can take the form of implicit or explicit threats of penalties for failure to agree to participate or for wishing to withdraw from participation. It can also take the form of excessive monetary or other personal reward (e.g., monetary compensation that is disproportionate to personal income) in exchange for study participation. Countries adopt this principle in varying ways. In Member States of the European Union, for example, regulatory authorities enforce laws forbidding incentives or financial inducements for minors or incapacitated adults unable to give consent.[97] Spain forbids participation stipends, permitting compensation only to working minors and targeted vulnerable subjects.[98]

A respect for human dignity, moreover, mandates that a clinical participant is treated as a human being, rather than quantified as a body in a clinical endeavor. Clinical trials require experimental subjects. However, the very epistemology of clinical trials is risk-laden—both for the subjects experimented upon, and for the research agents who invest huge amounts of money in a therapeutic molecule that may or may not eventually come to market. A form of structural violence of clinical experimentation emerges from the reality that it is a process that can only be set in motion by the risking of human subjects, and that clinical subjects are often incentivized by the promise of new, emerging therapies.[99] The model stands, then, to encourage the experimental subject to make her body available for experimentation, but then is rendered incapable of drug access after the trial concludes, even after a therapy's approval.[100]

An ethical clinical, trial, however, respects the need for access to therapy during a trial, and then, provides for such therapy following a trial's successful completion. This component of a feminist model can be informed by the theories of bio-ethicist Kaushik Sunder Rajan. According to Rajan, the common avenue for any sort of therapeutic access to experimental drugs is too often limited to 'compassionate use' programs of pharmaceutical companies, which make

[96] See *supra* note 19, Declaration of Helsinki; *supra* note 33, CIOMS Ethical Guidelines.
[97] Norman M. Goldfarb. *Laws, Regulations, and Clinical Trial Agreements,* Address at the Society of Research Administrators International 2004 Symposium. (2004).
[98] *Id.*
[99] *See, e.g.,* Nikolas Rose, THE POLITICS OF LIFE ITSELF: BIOMEDICINE, POWER, AND SUBJECTIVITY IN THE TWENTY-FIRST CENTURY 34 (2006).
[100] *Id.* At 34-35.

the drugs tested in Phase III trials available to the sick volunteers for a fixed period of time after completion of the trial.[101] No regulatory body involved in developing clinical-practice guidelines insists that drugs tested in underdeveloped regions of the world should be marketed there.[102] 'Ethics' in the distribution realm are provisional.

The uncoupling of experimental subjectivity from therapeutic access enrolls experimental subjects in the cause of health, offers them agency, but locates them outside a regime of long-term quality care.[103] In other words, some experimental subjects contribute in a significant sense to health by making themselves available as experimental subjects, but this is in no way linked to their own healthiness, or that of others in their class who might obtain access to new medication as a consequence of the risks to which the volunteers are exposed. In these cases, in which high-risk experimental subjectivity lacks potential for clinical benefit, the clinical testing model is inherently limited in design. A complete feminist model of clinical study incorporates beneficence and justice first, ensuring the consent of its subjects, but then, just as importantly, it ensures that clinical participation benefits volunteers.

Clinical trials invariably take the form of a social contract in which a small number of people are put on potentially risky medication for the sake of a larger social good—the development of new therapies.[104] However, those recruited into Phase 1 trials tend to be less well-off in comparison to those ultimately allowed access to the therapy, so that the social contract can never be a pure liberal one between groups of individuals.[105] Ultimately, even if all clinical trials conducted in developing countries adhered to the letter of the law and the spirit of ethical codes, the very structure of this trial would remain one of exploitation.[106] Too often, underdeveloped populations are used purely as experimental subjects, without the implicit social contract of eventual therapeutic access. In practice, there is no guarantee that an experimental drug tested on a local population will necessarily be marketed there after approval, let alone be made available at an affordable cost. However, in the event of successful development, a feminist, ethical trial model requires that the developed therapy will be accessible to its clinical participant group upon introduction to society. The requirement manifests first as access via the

[101] Kaushik Sunder Rajan, *Biocapital: The Constitution of Postgenomic Life.* 7 AM J BIO. 17, 16-31 (2007).
[102] *Id.* at 18.
[103] *Id.*
[104] Kaushik Sunder Rajan, "Biocapital: The Constitution of Postgenomic Life." *The American Journal of Bioethics*. Vol. 7, Iss. 6, 2007. pg.67.
[105] *Id.* at 72
[106] *Id.*

market; then, encourages research companies to opens forums for affordable, perhaps subsidized, access to a therapy to its subjects post-trial completion and approval.[107]

This type of model-driven market access infrequently occurs in the modern era. In 2002, for example, a study of more than 15,000 people in Uganda demonstrated ignorance of such ethical concerns. The study concluded that the risk of spreading AIDS through heterosexual sex rose and fell with the amount of virus present in the blood. The research was controversial not because of its conclusions, but because of its methodology. Unlike studies of HIV in developed countries, the volunteers in Uganda were not offered treatment, nor did doctors advise or provide preventative measures to the healthy spouse of an infected partner harboring the virus. The team merely tracked infected individuals and their partners from October of 1994 to 1998, examining the relationship between serum viral load, concurrent sexually transmitted diseases, and other known HIV risk factors. Ultimately, Quinn and colleagues determined that targeted therapies aimed at specifically decreasing vial load in serum could prove promising as HIV/AIDS therapy, but then, failed to offer the group they had targeted any method of access these therapies, or any other kind of intervention, in their lifetimes. Those who participated in the study never received any, especially low-cost, means to treat their conditions; moreover, doctors and aids neglected to ever advise preventative measures to decrease rates of transmission to uninfected partners or future offspring.[52]

The trial demonstrates just how voluntary research may manifest as unethical even-when retaining elements of informed consent. Both of the study's groups had initially agreed to be volunteers in clinical research. In Uganda, doctors never lied or misled these subjects. But they failed to offer any kind of access to the HIV/AIDS therapies on the market or in development. The example demonstrates that when clinical research is successful but lacks either one of the key components of a feminist model, it fails to treat its subjects with feminist, ethical consideration.

Case Study: The Oral Contraceptive

This part of my paper presents an answer to the series of questions I presented earlier: can a clinical trial be both ethical, legal, and feminist? And importantly, can a feminist, ethical trial be fiscally as well as ethically successful? To demonstrate that a feminist model of clinical

[107] *Id.*

research efforts can lead to successful, marketable developments, I analyze a case study of a clinical trial which incorporated a feminist understanding of an ethical trial into its clinical model, and then successfully marketed its clinical findings. This case study critiques the early trials of the oral contraceptive pill. Using the feminist model I constructed above, emphasizing women's needs for agency and access in clinical work, I demonstrate that the clinical trials of the first birth control pill employed standards set forth by modern international standards of research while incorporating components regarding agency, informed consent, and access of my constructed feminist model. It can be used today as a model for ethical, clinical research.

After giving some historical background, I organize my discussion into two components. The first component argues that the Puerto Rican women purposefully lived their clinical experience as partners with, and not tools of, the drug developers; they were aware of the dangers and benefits of their choices and acted with informed choice, and not coercion. The second component argues that, although the contraceptive trials progressed with the help of females from a comparatively developing country, these women and the groups they represented benefited from the ultimate drug design, and thus, were agents who contributed significantly to an effort which served their own interests.

A. Historical Background

When Gregory Pincus, the "father" of the birth control pill, decided to meet the challenge of finding a hormonal contraceptive, he entered unknown territory. Although chemists had begun to synthesize a number of compounds which appeared to have contraceptive qualities in the early 1950s, no one knew how to anticipate the effects these chemicals might have on the female body, or whether they would cause adverse reactions. The only way to find out was to test the pill on women themselves. The task was expensive, socially charged, and logistically daunting; it required the aid of numerous researchers and, most importantly, female volunteers.

Although initial theoretical and laboratory work was performed with a small group in Massachusetts, large-scale human study was made impossible in the United States by strict legal barriers of the era. As late as 1960, the American legal system was not hospitable to the idea of birth control. Thirty states had statutes prohibiting or restricting the sale and advertisement of

contraception.[108] The driving force behind the original anti-birth control statutes was a New Yorker named Anthony Comstock. Comstock, a devout Christian, began supplying the police with information for raids on sex trade merchants in the 1890s and came to political prominence with an anti-obscenity crusade. He soon identified the contraceptive industry as one of his targets. Comstock was certain that the availability of contraceptives alone promoted lust and lewdness.[109] He supplied Congress with an anti-contraceptive proposal he drafted himself; within three years, U.S. legislation at the federal and state levels rendered contraceptive drug design punishable by law Collectively known as the Comstock Laws, a total of twenty-seven pieces of legislation served as strong legal obstacles to the experimentation with and clinical association to contraceptive distribution or research. They prohibited the publication of any material associated with birth control, outlawed distribution of contraceptive means, and set heavy fiscal and punitive penalties on those who conducted research in the area.[110]

Katherine McCormick financed the first years of the drug's development and the initial drug studies. She was a woman devoted to the idea of finding a contraceptive method safe and available for all women everywhere, and was specifically determined to help further the idea of a affordable oral contraceptive which might be consumed in private to render a woman temporarily infertile.[111] For McCormick, it was imperative to find a simple control that was divorced from coitus, ideally a contraceptive pill which women could swallow at any time without a man's knowledge. She saw as the key to women's empowerment.[112] Despite her own eagerness to see the fruits of the project, she conveyed in correspondence a key understanding that both she and the team she financed, shared:

> Human females are not rabbits in cages. The latter can be intensively controlled all the time, whereas the human females leave town at unexpected times, cannot be examined due to time constraints, they forget or dislike to take medications—in which case, we must start all again over at once. Scientific accuracy must

[108] Nicola Beisel, IMPERILED INNOCENTS: ANTHONY COMSTOCK AND FAMILY REPRODUCTION IN VICTORIAN AMERICA. 134 (1997).
[109] *An American Experience: The Pill*. Transcript pg. 2: found online at http://www.pbs.org/wgbh/amex/pill/filmmore/ps_pincus.html.
[110] Beisel, *supra* note 82, at 119.

[111] Laura Marks, SEXUAL CHEMISTRY 18 (2004).
[112] M. Gray, MARGARET SANGER: A BIOGRAPHY OF THE CHAMPION OF BIRTH CONTROL 396 (1979).

> be maintained or the resulting data is worthless; in short, we need the full cooperation of our women.[113]

From the start, the researchers knew they needed to conduct such trials outside of Massachusetts because of the Comstock laws. In that state, those found breaking the Comstock laws faced penalties of up to five years in prison and fines of $1,000 on each occasion that contraceptive inquiry and devices were provided or developed.[114] Various possibilities were discussed; New York, Puerto Rico, Japan, Hawaii, India, and Mexico were each strongly considered. Puerto Rico was ultimately favored because directors of the University of Puerto Rico Medical School were trained in America, and Pincus expected them to conduct tests on vaginal tissue samples, endometrial biopsies and urine analyses in the same manner as his American team. Just as importantly, Puerto Rico was near enough to the US to enable close supervision by Pincus and his team, as the study's primary investigators.[115]

B. A Feminist Model I: Women Exercising Agency as Study Subjects

Ultimately, the first large-scale field studies were mounted in Puerto Rico in April of 1956.[116] While researchers considered Puerto Rico ideal for the tests primarily for its proximate location and its cooperative and similarly trained staff, the island was fitting for a number of other reasons. It already possessed a thriving family planning movement and well-established network of birth control clinics. As early as 1935, private humanitarian groups were advancing financial aid from the United States to start birth control in Puerto Rico.[117] An American-trained clinician concerned with the public health of his island, Dr. Clarence J. Gamble, along with a few affluent Puerto Ricans, organized and funded the Maternal and Infant Health Association in January, 1937, and opened twenty-two birth-control clinics in that country in fourteen months.[118] The government of Puerto Rico supported their effort; on May 15, 1937, the Legislative Assembly of Puerto Rico authorized the Commissioner of Health to:

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[113] McCormick to Sanger, 31 May 1955, Margaret Sanger's papers, Sophia Smith Collection, Library of Congress.
[114] C.R. McCarin, BIRTH CONTROL POLITICS IN THE UNITED STATES, 27-28 (1994).
[115] *Id.* at 33-34.
[116] Marks, Sexual Chemistry *supra* note 85, at 47.
[117] Nick Thimmesch, *Puerto Rico and Birth Control.* 30 JOURNAL OF MARRIAGE AND FAMILY, 246, 252-262 (1968).
[118] *Id.* at 254.

> ...[I]ssue a license to teach and practice eugenic principles in public institutions and centers, to physicians who are specialists in obstetrics, or to physicians who are not specialists, and to midwife nurses who pass an examination or who comply with the regulations prescribed for the purpose.[119]

The Commissioner could thereafter authorize persons to teach birth-control methods and distribute contraceptives to both married couples and those who "publicly live in concubinage." The 1937 laws dealing with birth control and abortion were readily signed by Acting Governor Menendez Ramos, who stated,

> I hope that the Insular Government will take active part in the dissemination of such information [modern birth control methods]. I think maternal clinics should be set up in all the large population centers of the island.[120]

In Puerto Rico's governing bodies, poverty and shortages of food and housing trumped the Catholic identity of the island. For two decades prior to the pill's trials, for example, the Puerto Rican Secretaries of Agriculture and Development directed funding for birth control clinics across the island in an attempt to manage the island's population growth, trying to address the food shortages and severe poverty that wrecked the island in the 1940s and 50s and that were strained further by an ever-growing populace.[121]

This was the climate in which Pincus and his team began to test improved contraceptive measures, and it was this growing population and chronic poverty that predisposed the women of Puerto Rico to be open to new birth control methods despite that fact that many were faithful to a Catholic identity.[122] The women themselves came from various classes and backgrounds, and did not possess uniform training or educational identities. Some were teachers, others were nurses; many were secretaries and still more worked as saleswomen and traders. They comprised a model which demonstrated that the pill could be used by a diverse group of women in terms of

[119] *Id.* at 253.
[120] *Id*. at 254.
[121] Marks, *Sexual Chemistry*, *supra* note 85, at 102-104.
[122] *Id.* at 105-06.

education and occupation, from those who lacked medical training to those who lacked formal schooling altogether.[123]

The trials demanded a high degree of effort and cooperation. The trial volunteers had to be willing to commit to several months of complicated lifestyle rules and intense scrutiny, climaxing in a series of surgical interventions.[124] Failure to comply would present significant data lapses to the clinical study. So, during these trials, researchers instructed women to follow very complicated and time-consuming routines. Besides being required to take hormone tablets, each woman had to take her own body temperature readings and vaginal smears on a daily basis.[125] Every woman also had to collect urine once a week for an entire day to be given to the researchers for hormone analysis.[126] This procedure was particularly burdensome: it required a woman to be within easy reach of a toilet and special collection and analysis supplies. In addition, a third of the participants had to consent a monthly endometrial biopsy.[127] These biopsies involved taking a tissue sample from the womb lining, a procedure which is at best uncomfortable and at worst extremely painful. Some women were given laporatomies (open abdominal surgery to observe directly ovarian and uterine changes) on the twenty-third day of their cycles. All of these cumbersome procedures were designed to determine whether the compound effectively suppressed ovulation, and therefore had contraceptive potential.[128] As Katherine McCormick wrote to trial co-sponsor Margaret Sanger in June of 1954,

> I find incredulous the headache of these tests and the cooperation of the women patients...there is so much (testing) and it must be accurate. I really do not know how it is obtained at all—it is so onerous, it really is—these women attend so carefully, however, and so persistently."[129]

In later correspondence, McCormick marvels at the women of Puerto Rico, detailing incidents in which she visited sites with Rock to see women asking questions about their side effects and asking permission to take anti-nausea or pain relief medicine in conjunction with

[123] *Id.* at 108-110.
[124] *Id.*
[125] *Id.* at 105.
[126] *Id.*
[127] *Id.* at 108.
[128] *Id.* at 105.
[129] MS-SS, 19 July 1954, Letter 43.

their contraceptive pills. She admires one woman's dedication in having her literate grade-school daughter help her record daily dosages and meticulously count out the requisite five rest days between pill cycles.[130]

The twenty-member research team encouraged this active participation, instructing women from the start to bring all concerns and questions to the doctors' attention and helping them to understand the practices mandated by their participation in the trials. Each woman's consent and understanding was carefully acquired. At the commencement of the trials, each of the trial's requirements was explained, in English or through local translators.[131] Women had to agree to the procedures, and before obtaining new pills, had to agree and give willing consent again. The early trials in Puerto Rico did not involve signed forms of consent, but as Dr. Lugli Mastroianni, a member of the ground team, recalled later in the 1980s,

> The concept of informed consent that is so talked about now, and is a legal requirement of any research project involving human volunteers today, didn't exist then [during the oral contraceptive trials]. But Rock practiced it before it was even defined. There were...long discussions of the risk factors with each volunteer, and we were told to welcome both their feedback and their concerns, any time during the trials. It didn't matter that Rock had no formal guidelines, he set his own—they were high standards indeed.[132]

As Mastroianni indicates, the regulatory bodies which are today responsible for ensuring ethical clinical protocol did not exist in the 1950s. "Informed consent" was a term, in fact, that was not yet coined. However, the oral contraceptive trials were characterized by a theory of informed consent that could meet the international standards of today, and serve as example of the kind of consent to achieve in a feminist, ethical trial setting. The trial's model required that participants receive adequate information concerning the project's aims, methods, expected benefits, and potential hazards and discomforts, at its commencement, and then, at each stage in

[130] M. Gray, *supra* note 86, at 394-9.
[131] Marks, *supra* note 102, at 122.
[132] Loretta McLaughlin, THE PILL, JOHN ROCK, AND THE CHURCH: THE BIOGRAPHY OF A REVOLUTION 117 (1982).

its progression.[133] Furthermore, each of the woman subjects was informed that they were free to withdraw their participation at any time, without any risk.[134] Rock and his researchers explained the terms, commitments, benefits and dangers in a straightforward way to these participants, in a language accessible to the Puerto Rican women. They provided that each participant understood the importance of the information and was fully capable of making a decision. The oral contraceptive trial set-up gave each volunteer deliberation time before deciding whether or not to participate, and then provided information for subjects at their request, or when trial conditions change, throughout a trial. Each month, every woman had the opportunity to cease participation.

Rock's ethical concerns were mirrored in the conduct of the man who led the team of researchers in Puerto Rico. Though legally unnecessary, Celso Ramon Garcia similarly strove to execute a project with the full consent and commitment of his participants.[135] Garcia was particularly concerned with the medical side effects and yet-unknown consequences of taking the pill. Therefore, he insisted that certain tests be performed on the patients during the trials, such as investigations for liver functioning, Pap smears, and tests for blood clotting.[136] These investigative tests became increasingly important for both the women and the researchers, catching negative side-effects early, especially as time went on and the scientists learned about the dangerous effects, like blood clotting and stroke, incident to higher dosages.[137] His approach lent the women's consent a more sophisticated meaning. Garcia approached a trial in such a way as to treat consent as an ethical state of a study rather then a static commencement agreement; his regular physicals ensured that each participant was kept abreast of the health impacts from her participation in the study.[138]

In the age of the pill's development, before the dawn of international ethical guidelines and modern regulatory agencies, clinical trials generally lacked thorough attempts of careful oversight.[139] Garcia's actions, however, were born of a personal sense of responsibility—he

[133] *Id.* at 23. *See also, supra* note 33, CIOMS Ethical Guidelines, at 48; *see also* Beaqueart, *infra* notes 74,75.
[134] McLaughlin, *supra* note 132 at 50.
[135] Interview with Garcia, pp. 29-32, found in Lara Marks, *Sexual Chemistry*, pgs. 113-117.
[136] *Id. at* 114.
[137] Paul Vaughan, THE PILL ON TRIAL, 49 (1970).
[138] Helen Bequaert Holmes. *Rights over One's Own Body: A Woman-Affirming Health Care Policy*, 3 HUMAN RIGHTS QUARTERLY, 74, 71-87 (1981).
[139] *Id.* at 51-53. (Testing the safety and effectiveness of new drugs were not established features of international clinical trials until the late 1960s, after regulatory bodies began to respond to events like the thalidomide scandal in Europe (See *supra* note 2). For example, in 1959 (two years into the pill's series of trials) one pharmaceutical

reveals in an interview that he felt a duty to "ensure good health care" for the women in the trials in Puerto Rico.[140] He describes that many of the trial participants lacked access to quality health care services outside of the trial, and were often side effects like dizziness and nausea.[141] He further describes that he developed a special concern for the drug's potential ability to damage reproductive functions, or cause infertility.[142] As a result, he determined it clinically appropriate to require his team to perform physicals and medical examinations on the trial subjects at least twice a month.[143]

The trial's success with constructing ethical, feminist forms of consent and communication is also reflected by the deference with which the scientists treated the participant's self-reports.[144] Their technical data sets were supplemented by the woman's voices.[145] Throughout the early months of the pill's testing, clinicians relied on testimony of the four hundred women during on-going consent discussions to steer reconfiguration of the pill's drug make-up. Pincus later held that the trial process would not have evolved but for the researchers' incorporation of women's reports.[146] They highlighted initial problems of nausea; then, sporadic breakthrough bleeding and headaches; finally, dizziness, changes in blood pressure and odd pains—complaints that inspired clinical suspicion of increased potential for blood clotting.[147] Candid reports of such conditions led to changing amounts of the synthetic hormones in the pill.[148] The subjects' testimony was thorough because their consent and authentic cooperation had been sought and then maintained.

Over four hundred Puerto Rican women participated in the first drug trial of the oral contraceptive. Several of the women were coping with large families of small children; they took time from busy lives of myriad responsibilities to travel long distances and keep painstaking records of their experiences on the pill. Women came to the project in an effort to control this aspect of their lives. As one subject, Julia, explains,

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company, Beachams, was approved to launch a new antibiotic after only having conducted two weeks of toxicity tests, without any record of having performed any physical examinations on participants.)

[140] Interview, *supra* note 97 at 30.

[141] *Id.* at 31.

[142] *Id.*

[143] *Id*. at 32.

[144] Bequaert, *supra* note 85, at 11.

[145] Bequaert, *supra* note 85, at 12-14.

[146] Marks, *supra* note 85, at 109.

[147] *Id.*

[148] L. Marks & White Junod, *Women on Trial: Approval of the First Oral Contraceptive in the United States and Great Britain*, 28 J HIS MED 54, 56 (1998).

> I am thirty, have ten children, aged sixteen to ten months. My husband is very ill, drinks heavily and makes life difficult. I do odd jobs to support the family, and me and my husband do [have daily intercourse] but he won't let me use contraception. I've been using this medicine a whole year, and got through the whole year….with no baby![149]

Ultimately, the clinical model in Puerto Rico provided its participants the opportunity to secure full information, at every stage during their experience, in a beneficent way. The pill's clinical research team considered women's unique bodies and understanding within scientific discourse, and treated the patients involved in their medicine as partners rather than passive witnesses. Theirs was an ethical, feminist approach to clinical practice, one allowing their women participants to make fully informed choices amidst the multidimensional concerns of their lives. The leaders of the research established the procedures and rules of their trial in such a way as to have the researchers themselves and the clinicians on the ground available to the subjects throughout the trial, answering questions, attending to problems, and providing medical assistance with diligence. In behaving in such an accessible manner, maintaining a dialogue with subjects ensuring informed consent, the clinical directors embodied an ethical approach to the trial that would satisfy that of a feminist model of clinical ethics.

The evidence of informed consent and ethical clinical practice does not singularly support my claim that these trails were conducted with components of a feminist clinical approach. Importantly, as I argue next, this practice of securing informed consent was complemented by the trial's component of access.

C. A Feminist Model II: Women Reaping Fruits of their Labor

Moving from evidence of informed consent and agency among the female participants involved with the pill's testing, I will now argue that the contraceptive trials followed an ethical model in that the pill was a drug that benefited those who participated in the furthering of the pill's research.

[149] Vaughan, *supra* note 109 at 49.

In general, research agendas reflect the interests, power, and privilege of the elites who set them; they are seldom defined by the health needs or interests of those who are most marginalized in society.[150] These kinds of clinical studies produce knowledge that strengthens the health and opportunity of those who are already well placed in society, and often ignore the needs of the disadvantaged. Clinical participants are often granted access to therapies during clinical discovery trials, for example, and then precluded from accessing therapies once they are reviewed and marketed.[151]

The clinical trails of Puerto Rico, in contrast, allowed for ready access to the birth control pill: the country's underdeveloped populations were not used purely as experimental subjects. After the drug's regulatory approval, the women were granted therapeutic access to the first contraceptive drug available. In practice, the researchers did not personally distribute pills to individual clinical participants; however, the pharmaceutical company with whom the researchers contracted to develop and market the pill, Searle, worked with the researchers to direct the pill back to Puerto Rico.[152] The pill, then, was accessible to the female participants of the contraceptive studies, and to the other women of the country.

Part of the reason the drug developers could direct the pill's market distribution to facilitate participant assess lay in the nature of its niche therapeutic use. Enovid passed the FDA's tests on June 17, 1958,[153] and, in the jargon of the industry, was advertised as an "ethical specialty:" it was advertised to doctors and sold in prescriptions, not directly to the general public.[154] Though it was not advertised directly to customers, doctors like Pincus, Rock, and Garcia had a great deal of leverage as to which physicians, including those operating in the subsidized birth control clinics of Puerto Rico,[155] could be convinced to proscribe the drug initially. The pill's researchers, then, responded to their trial participant's needs for access to therapy after their trial, providing for the therapy following a trial's successful completion. This kind of physician-based distribution ensured that the therapeutic access to experimental drugs

[150] See *supra* notes 22, 23.
[151] See *supra* notes 48, 49.
[152] Vaughan, *supra* note 109 at 55-57. (Searle was an American pharmaceutical corporation; the pill's first form was marketed under its trade name, Enovid. The United States had an agency for approving new drugs at this time, the Food and Drug Administration, but the agency was weak, concerned primarily with food imports, and lacked the strict guidelines it wields today.)
[153] See *supra* note 115.
[154] A.F. Guttmacher, "The Pill Around tile World," IPPF Medical Bulletin, Guttmacher Papers. 1966.
[155] See *supra* note 83.

wasn't limited to a 'compassionate use' program, either, which would have made the drugs available to the volunteers for a fixed period of time after completion of the trial.[156]

A key element of the clinical participant's access opportunities lay in the fact that half of the expense of pill proscriptions was borne by the Department of Health of the Commonwealth of Puerto Rico.[157] This distribution of funding was directed away from governmental subsidizing of the foam contraceptive called Emko, a contraceptive then determined to be only 70 percent effective.[158] So in terms of Puerto Rico's capacity to provide birth control to those seeking it, a newly appropriated annual funding of $500,000 per clinic in 1958 lowered a patient's monthly costs to less than 25 percent of market expense, or a third of a day's median wages for the average 30-yr-old female in Puerto Rico in 1959.[159] In addition, the government sponsored an information campaign for the pill. Handbills, comic books, pamphlets, and a newsletter titled "The Right to Happiness" were distributed across the island.[160]

The readers of Puerto Rico were reached through such materials. For those who could not read and knew no one who could, the government sponsored civic group-run community forums, where respected community groups brought together the spokesmen of clinics and sometimes the government's Department of Health in familiar community spaces, responding to residents of the community during question-and-answer sessions.[161] After adjusting for population numbers, the women of Puerto Rico used the pill in proportional numbers to the women, both white and black, of America in the years following its market release.[162]

Ultimately, the trials of Puerto Rico became rather widely publicized, mostly by anti-contraceptive groups.[163] Thousands of women in the United States and Europe, aware of the trials and the FDA deliberation, impatiently waited for the chance to try it. Upon approval in the U.S. and Britain, after continued, successful use in Puerto Rico, it quickly arrived in Haiti, Latin

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[156] Kaushik Sunder Rajan, *Biocapital: The Constitution of Postgenomic Life.* 7 AM J BIO. 17, 16-31 (2007).
[157] Nick Thimmesch. "Puerto Rico; Family Planning and Fertility Control." 30 *Journal of Marriage and Family*, 261 (1968).
[158] *Id*. at 289.
[159] *Id.*
[160] *Id.* (The materials even appealed to the religious feeling of ardent Catholic Puerto Ricans. In the forward of "The Right to Happiness," the question is posed: "If God has given man intelligence he has not given to birds, shouldn't you make the best plans so your family will consist of the number of children which you can take care of, feed, and educate properly?")
[161] *Id.*
[162] J. Reed, THE BIRTH CONTROL MOVEMENT AND AMERICAN SOCIETY. 78-79. (1993).
[163] Bernard Asbell. THE PILL: A BIOGRAPHY OF THE DRUG THAT CHANGED THE WORLD. 108 (1995). See also: *The Pill, An American Experince.* Transcript available at: http://www.pbs.org/wgbh/amex/pill/filmmore/fr.html.

American nations, Copenhagen, and Japan.[164] Family planning clinics and doctors alike had access to the pill and readily distributed prescriptions. Interestingly, limitations to access were never found in comparatively poor or developing economies. The places with the greatest access challenges were those rich with conservative values, like the American states of Kentucky and South Dakota.[165]

The oral contraceptive trials were characterized by the complete feminist model of clinical study. The trials incorporated beneficence, human dignity, and justice, ensuring the consent of trial subjects, and just as importantly, ensuring that clinical participation benefited the female volunteer participants. The uncoupling of experimental subjectivity from the subsequent therapeutic access of the oral contraceptive offered the clinical participants a chance to contribute in a significant sense to their health by making themselves available as experimental subjects, and linked this participation to their own long-term benefit, and that of others in their community who might obtain access to new medication as a consequence of the risks to which the volunteers and their families were exposed. The feminist model design of the trial demonstrates that ethics, regulations, and market initiatives can combine in a feminist framework, and that successful drug therapies can result from international clinical discovery that allows their women to experience all the elements of a feminist, ethical clinical model.

Conclusion and Recommendations

A woman coming into the health care system is a unique individual psychologically and physically. Every aspect of her health and well-being should be acknowledged, and her contributions to the discourse around her clinical participation, through both concerns and positive feedback, should be incorporated in a model of her health interests. An ethical, feminist research model that upholds the modern ethical standards of international clinical discovery should further be characterized by a negotiation between subjects and investigators that maintains full and informed consent methods, and ensure that subject groups ultimately benefit from access to a treatment's scientific inquiry.

When analyzing the clinical trials of the pill in Puerto Rico with this model, the clinical-research landscape demonstrates that a model can be ethical while feminist, and ultimately, a

[164] E. Rice-Wray, "Oral Contraception in Latin America," Proceeding of the Seventh International Conference on Planned Parenthood, Singapore, Feb. 1963 (reprinted from Excerpta Medica International Congress, Series No. 72.)
[165] Vaughan, *supra* note 109, at 62-67.

successful marketing endeavor. The oral contraceptive pill is and always has been an indisputable clinical goldmine: at any given moment, over 100 million women worldwide are using the oral contraception, and the average user takes the pill for almost twelve years of her life.[166]

Looking forward to future international clinical endeavors, I propose two specific recommendations to augment the contemporary guidelines for international clinical drug development. Regulatory bodies of nations should require those seeking market approval for new drugs and treatment methods to utilize a feminist clinical model, and adopt funding protocols incentivizing adherence to specified ethical standards in research. Using legal and fiscal incentives, international clinical endeavors should promote an ethical, feminist experience, allowing for, specifically, components of true consent and therapy access.

Regulatory bodes should require that trial developers construct and implement a process for consent that addresses women's information needs and questions at the commencement of trials, and in addition, incorporate supplemental consent discussions at periodic times during a trial. These consent discussions should invite a woman's specific feedback explaining her experience in the trial endeavor and encourage women to express developing concerns with any element of the trial or clinical experience. While treating women within the feminist, ethical framework, these conversations further the success of clinical trials as they allow clinical researchers to obtain important information about the efficacy of new drugs and interventions in the context of women's physiology. With such knowledge, researchers can design therapies that respond to women's specific needs and thus allow women to derive equal benefits from the scientific discovery process.

Regulatory bodies should also encourage scientific researchers to facilitate access to drug therapies post-clinical development and approval. Women who dedicate their bodies and their experiences to clinical discovery must be allowed access to the therapies they forward. Without this opportunity, women's bodies are quantified as tools of experiments, rather than valued in the way that international ethics guidelines dictate, that is, according to the principles of beneficence, justice, and human dignity. Ultimately, I recommend that the next stage in the progressive development of international clinical regulation should be to promulgate feminist considerations

[166] James Trussell. *Contraceptive Efficacy*. 131 ARCH DERMATOL 1064, 1067-68 (1995).

in clinical efforts, ensuring informed consent and a participant's access to therapies after clinical participation.

Works Cited

Journal Articles

E.J. Cassell. The Principles of the Belmont Report Revisited. How Have Respect for Persons, Beneficence and Justice Been Applied to Clinical Medicine? 30 HASTINGS CENT REP 12 (2000).

Maria Teresa Ruiz Cantero & Maria Angeles Pardo. European Medicines Agency Policies for Clinical Trials Leave Women Unprotected. 60 J EPIDEMIOL COMMUNITY HEALTH. 911 (2006).

Rebecca Dresser, Wanted: Single, White Male for Medical Research, 22 HASTING CET. RP. 24 (1992).

Scot A. Fritzen. 83 Reorienting Health Ministry Roles: Capacity and Strategy Gaps. 83 HEALTH POLICY 73 (2007).

J.T. Fullerton, Issues in Clinical Trials Management; Women In Clinical Trials 1950–1993: From Exclusion to Equity. 49 RES NURS. 1 (1995).

Bernadine Healy, Women in Science: from Panes to Ceiling, SCI. 67 (1992).

Helen Bequaert Holmes. Rights over One's Own Body: A Woman-Affirming Health Care Policy, 3 HUMAN RIGHTS QUART., 74 (1981).

Jeannette R. Ickovics & Judith Rodin, Women and AIDS in the United States - Epidemiology, Natural History, and Mediating Mechanisms, 11 HEALTH PSYCHOL. 110 (1982).

M.A. Grodin. Legacies of Nuremberg: Medical Ethics and Human Rights. 73 JAMA 1676 (2003).

R.H. Kampmeier. The Tuskegee Study of Untreated Syphilis. 65 SOUTH MED J. 1243 (1972).

James v. Lavery, Monitoring and Oversight in Critical Care Research, 8 CLINICAL CARE 403 (1993).

Niels Lynoe, Mikael Sandlund, & Lars Jacobsson, Informed Consent: Study of Quality of Information Given to Participants in a Clinical trial. 303 BMJ 14 (1991).

L. Marks & White Junod, Women on Trial: Approval of the First Oral Contraceptive in the United States and Great Britain, 28 J HIS MED 54 (1998).

Vanessa Merton, The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. Women) from Biomedical Research.13 AM. J OF LAW & MED. 114 (1993).

Charles R. McCarthy. Historical Background of Clinical Trials Involving Women and Minorities 69 ACADEMIC MEDICINE 695 (1994).

Chiara Melloni, Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention. 3 CARDIO OUTCOMES 135 (2009).

M.N. Prout. Participation of Women in Clinical Trials of Drugs Therapies: A Context for the Controversies. 3 MED GEN MED 60 (2001).

Kaushik Sunder Rajan, Biocapital: The Constitution of Postgenomic Life. 7 AM. J. BIO. 17 (2007).

Nick Thimmesch. Puerto Rico; Family Planning and Fertility Control. 30 J. OF MARRIAGE AND FAMILY 261 (1968).

James Trussell. Contraceptive Efficacy. 131 ARCH. DERMATOL. 1064 (1995).

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. J. AM. MED. ASSOC. 40 (2000).

H. Yanagawa. Clinical Trials for Drug Approval: A Pilot study of the View of Doctors at Tokushima University Hospital. 53 J. MED. INVEST. 290 (2006).

Books & Reports

Bernard Asbell. The Pill: A Biography of the Drug that Changed the World (1995).

T.L. Beauchamp, Contemporary issues in bioethics (2nd ed. 1982.)

Nicola Beisel, Imperiled Innocents: Anthony Comstock and Family Reproduction in Victorian America (1997).

Dept. of Health Education and Welfare. National Commission for the Protection of Humans Subjects in Biomedical and Behavioral Research. Pub. No. 76-127: RESEARCH OF THE FETUS (1975)

Lionel D. Edwards, Design and Conduct of Research in Women: To Include or Exclude: A Pharmaceutical Industry Physician's Perspective (1994)

Allen Hornblum, Acres of Skin: Human Experiments at Holmesburg Prison (1998).

M. Gray, Margaret Sanger: A Biography of the Champion of Birth Control (1979).

John Griffin, The Textbook of Pharmaceutical Medicine (6th ed. 2009).

11 Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law (1949)

Laura Marks, Sexual Chemistry (2004).

C.R. McCarin, Birth Control Politics in the United States (1994).
Loretta McLaughlin, The Pill, John Rock, and the Church: The Biography of a Revolution (1982).

Johannes Morsink, The Universal Declaration of Human Rights: Origins, Drafting & Intent (1999).

Margaret Liu & Kate Davis, A Clinical Drugs Manual from the Duke Clinical Research Institute. (2nd. ed. 2010).

J. Reed, The Birth Control Movement and American Society (1993).

Nikolas Rose, The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century (2006).

Carol Tavris, The Mismeasure of Women (1992)

Paul Vaughan, The Pill on Trial (1970).

J.R Williams, The Declaration of Helsinki and Public Health. BULLETIN OF THE WORLD HEALTH ORGANIZATION (2008).

World Medical Assembly, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (18th ed. 2008).

Kay Weiss, Seizing our Bodies: The Politics of Women's Heath (Claudia Dreifus ed., 1978).

Women and Drugs: a New Era of Research 489 (Barbara Ray & Monique Braude eds., 1986).

Department of Health, Education, and Welfare. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1978).

Magazine & Newspaper Articles

Gina Kolata, AIDS Research on Drugs Bypasses Addicts and Women, N.Y. TIMES, Jan. 5, 1988.

Caroline Mallan, MDs Assume Men Need Better Care, TORONTO STAR, July 26, 1991.
Ellen Goodman, A Health-Research Bias. BOSTON GLOBE. June 21.1990.

Scott Greenberger, Science Friction: The Struggle of Female Researchers at NIH, WASH. POST, July 11,1993.

Medicine: The Thalidomide Disaster. TIME. Aug. 19, 1962.
Justin McCurry. Japan Unveils Plan to Boost Clinical Research. 369 LANCET: 1333 (2007).

Drug Testing on Men Only, WASH. POST., Dec. 8, 1992

Robert Walker, Heart Studies Ignore Women, CALAGHERY HERALD, Oct. 19, 1991.
E. Emanuel & C. Grady. The 2000 Revision of the Declaration of Helsinki: A Step Forward or More Confusion? LANCET, Sept. 30, 2001.

Lindsay Van Gelder, The Importance of Being Eleven: Carol Gilligan Takes On Adolescence, MS., July-Aug. 1990.

Statutes

Dept. of Health and Human Services Food and Drug Administration. Human Subject Protection Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application. 21 CFR 312. (2008).

Federal Policy for the Protection of Human Subjects. 45 C.F.R. §§ 46.101. (1991).
The Food and Drug Administration. 21 C.F.R. 5 10.90(b) (1993).

International Documents

Council for International Organizations of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002

European Parliament: Council on the Good Clinical Practice in the Conduct of Clinical Trials. Clinical Trials Directive, 2001/20/EC, April 4, 2001.

Directive 2001/20/EC of the European Parliament and of the Council of Europe (April 4, 2001).

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Guidelines. November 19, 2005. (Available online at http://www.ich.org/cache/compo/1.html (accessed April 21, 2011).

The International Covenant on Civil and Political Rights. art. 7. U.N. Doc. A/6316 (Mar. 23, 1976)

Report of the Fourth World Conference for Women: Beijing Declaration and Platform for Action. U.N. Doc. A/CONF.177/20/Rev.1. Sept. 15, 1995.

Universal Declaration of Human Rights, G.A. Res. 217 (III) A, U.N. Doc. A/RES/217(III) (Dec. 10, 1948)

Speeches & Transcripts

An American Experience: The Pill. Transcript pg. 2: found online at http://www.pbs.org/wgbh/amex/pill/filmmore/ps_pincus.html.

Norman M. Goldfarb. Laws, Regulations, and Clinical Trial Agreements, Address at the Society of Research Administrators International 2004 Symposium. (2004).

E. Rice-Wray, "Oral Contraception in Latin America," Proceeding of the Seventh International Conference on Planned Parenthood, Singapore, Feb. 1963 (reprinted from Excerpta Medica International Congress, Series No. 72.)

World Health Organization (WHO) Council for International Organization of Medical Services (CIOMS) International Guidelines for Biomedical Research involving Human Subjects. Introductory Comments. Nov. 13, 1982.

Letters

Margaret Sanger's Papers, Sophia Smith Collection, Library of Congress.