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Closing the Gaps in Human Subject Research Law: Regulating Clinical Research Conducted Outside of the United States

*Jennifer S. Bard, J.D., M.P.H.**

I. INTRODUCTION

The Declaration of Helsinki, which expresses an international consensus on the ethical conduct of human subject research, declares that “[m]edical progress is based on research that ultimately must include studies involving human subjects.”¹ Yet the pursuit of this progress has, unfortunately, been one marked by repeated instances in which individuals have suffered unreasonable and often unconsented to harm in pursuit of knowledge intended to serve the greater good.

The history of medical research is one of repeated instances in which individual subjects have suffered harm in the pursuit of acquiring knowledge that is purportedly intended to increase the public’s welfare. Looking just to the recent history of human subject research in the United States over the past fifteen years, we see repeated examples of good intentions leading to unimaginable, and irreparable, harm.² Although it is difficult to know how many people die every year as a direct result of their participation in research trials, the number may well run into the thousands.³ To suggest that there needs to be further oversight of human

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1. World Medical Association, WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, <http://www.wma.net/en/30publications/10policies/b3/>.

2. See Robin Fretwell Wilson, *The Death of Jesse Gelsinger: New Evidence of the Influence of Money and Prestige in Human Research*, 36 AM. J. L. & MED. 295 (2010); Diane Hoffman & Karen H. Rothenberg, *Whose Duty is it Anyway?: The Kennedy Krieger Opinion and its Implications for Public Health Research*, 6 J. HEALTH CARE L & POL’Y 109 (2002); Barbara A. Noah, *Bioethical Malpractice: Risk and Responsibility in Human Research*, 7 J. HEALTH CARE L & POL’Y 175 (2004).

3. See Noah, *supra* note 2, at 176 (“Although calculating the number of research-related

subject research is not to criticize the personal ethics of the scientists doing that research. There seems to be an inevitable, and in some ways inexplicable, process in which research, which seems reasonable while it is being done, is later exposed as unacceptably risky.⁴

Faced with the reality of both its inherent dangers and the seeming impossibility of accurately appreciating the extent of these dangers as they are occurring, the United States enacted the Medical Research Act of 1974, which is now often referred to as “The Common Rule” because it has been adopted by most federal agencies. Although a dramatic achievement in protecting subjects, the Common Rule is at once excruciatingly complex for those entities that are bound by it and provides no oversight for human subjects of research neither funded by the federal government or part of a clinical trial to sell a product requiring the approval of the Food and Drug Administration (“FDA”).⁵ Proposed rules announced by the Department of Health and Human Services (“HHS”) on July 22, 2011, address some of these concerns, but fail to close the gap caused by the lack of U.S. oversight for human subject research conducted outside the borders of the United States. Indeed, it is quite possible that the new regulations will increase the amount of research conducted overseas as costs for studies involving human subjects rise.

II. CURRENT REGULATION

A. *In the United States*

Currently, unless it directly funds or oversees it, the U.S. law does not directly regulate human subject research conducted overseas because the controlling legal scheme only covers human subject research funded or regulated by the federal government. This research falls under the jurisdiction of 45 C.F.R. 46, which is often referred to as “The Common Rule”⁶ for the protection of human subjects because it has been widely adopted by the many different federal agencies that conduct human subject

deaths and injuries has proven difficult, one expert suggests that as many as 5,000 people die annually in federally-funded research protocols, while tens of thousands more suffer injuries. Injuries in privately-funded research remain even more difficult to estimate due to the lack of any unified tracking system.”); Adil E. Shamoo, *Adverse Events Reporting- The Tip of an Iceberg*, 8 ACCOUNTABILITY IN RES.197 (2001).

4. See generally JONATHAN D. MORENO, *UNDUE RISK: SECRET STATE EXPERIMENTS ON HUMANS* (2000) (discussing a history of human subject research including the radiation studies of the 1950’s, the Army’s LSD studies of the 1960’s and the study of the natural history of syphilis conducted by the U.S. Public Health Service through Tuskegee University which was conducted in the United States which later was identified as unethical).

5. National Research Service Award Act of 1974, Pub. L. No. 93-348, 88 Stat. 342 (1974).

6. 45 C.F.R. § 46.101-124 (2009).

research. While federal funding for research comes from many different agencies, the primary source for medical research comes from funds Congress allocates and awards through competitive grants offered by the National Institutes of Health (“NIH”). In fiscal year 2010 the NIH oversaw a budget of thirty-one billion dollars, which was for the most part distributed to research universities.⁷

In contrast, participants in privately funded research occurring within the United States are protected only by existing common or statutory laws that govern everyday behavior. For research harm resulting from a research study, this means claims can be brought based on torts, contracts or even criminal law. Almost all states have some laws directly applicable to human subject research, but they are scattered across a number of different categories such as privacy, including access to genetic information, and often do not make distinctions between treatment and research.⁸ Some states have adopted, in whole or in part, the Common Rule as controlling law for research occurring within their jurisdiction,⁹ but only Maryland and Virginia extend the Common Rule to all human subject research conducted in their states regardless of funding source or type of study.¹⁰ California¹¹ and New York¹² have enacted laws, which provide broad protections for human subjects, but do not go so far as to adopt the Common Rule.

In an effort to close the gap between regulated and unregulated research, the newly proposed regulations extend the Common Rule to all research conducted at institutions which receive any federal research support.

The newly proposed regulations by HHS seek to do two perhaps inherently contradictory things: “to simultaneously enhan[ce] protections for research subjects and improve[e] the effectiveness of the federal oversight system.”¹³ In so doing, the regulations close at least one major gap

7. Testimony of Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health Supporting FY 2010 Budget Request (Apr. 28, 2010), <http://www.nih.gov/about/director/budgetrequest/fy2010testimony.pdf>. See also Paul Basken, *NIH Will Give Less and Demand More in 2010, New Leader Says*, CHRON. HIGHER ED., Jan. 17, 2010, available at <http://chronicle.com/article/NIH-Will-Give-LessDemand/63537/>; NIH Research Portfolio On-line Reporting Tools (June 24, 2011), <http://report.nih.gov/reportmap.aspx> (includes a discussion of the specific amount NIH provides each university).

8. See NAT’L. CANCER INST. CANCER DIAGNOSIS PROGRAM, 50-STATE SURVEY OF LAWS REGULATING THE COLLECTION, STORAGE, AND USE OF HUMAN TISSUE SPECIMENS AND ASSOCIATED DATA FOR RESEARCH (2004), available at <http://cancerdiagnosis.nci.nih.gov/pdf/50StateSurvey.pdf>.

9. See Edward P. Richards III, Louisiana State University, Medical Research and Human Experimentation Law, <http://biotech.law.lsu.edu/research/>.

10. See *Id.*

11. See Univ. California-Irvine, Ethical Guidelines, Federal Regulations, and State Statutes (Aug. 16, 2011), <http://research.uci.edu/ora/hrpp/ethicalguidelines.htm#state>.

12. N.Y. PUB. HEALTH LAW §§ 2440 - 2446 (2010).

13. Ezekiel J. Emanuel & Jerry Menikoff, *Reforming the Regulations Governing*

by extending the Common Rule to all research sponsored by a university that received any federal funding regardless of whether the specific project is itself directly funded by the government.

In so regulating, HHS exercises the power granted the federal government by the Supreme Court in *Rumsfeld v. Forum for Academic and Institutional Rights* to require universities to comply with federal directives if they receive not just direct federal funding for research, but also if they enroll students who receive federal financial aid.¹⁴ Since this essentially incorporates all but a handful of institutions of higher education, it provided the federal government with very broad authority to regulate activities on college and university campuses.¹⁵ Bringing all research done at universities under the Common Rule is a substantial achievement, but it still leaves major areas unregulated and in some ways could make things worse. This is because the newly proposed regulations leave untouched human subject research conducted by private companies that do not intend to use their results in a way currently regulated by the federal government. As the laws are currently written, those who serve as subjects in overseas drug tests are not protected by the same laws that in the United States would ensure their voluntary consent and on-going safety. Although the FDA stands in the position of goal keeper between the U.S. public and those who wish to sell a drug, the agency lacks not only the resources, but the legal authority to oversee the safety of every individual who takes part in the tests and clinical trials, on which applications for approval of a new drug are made.¹⁶

B. Internationally

We do not know how much human subject research is conducted overseas by U.S.-based companies or by companies that market drugs within the United States; however, there is no question that these studies are taking place in large numbers.¹⁷ According to Dr. Seth Glickman, a vocal critic of this practice, “there are powerful forces luring clinical trials overseas, including the lower cost of doing business and access to larger

Research with Human Subjects, NEW ENG. J. MED., July, 25, 2011, at 1.

14. *Rumsfeld v. Forum for Academic & Institutional Rights, Inc.*, 547 U.S. 47, 59 (2006) (holding that private universities must allow military recruiters on campus or risk eligibility for all federal funding).

15. See Loet Leydesdorff & Henry Etzkowitz, *The Transformation of University-Industry-Government Relations*, ELECTRONIC J. SOC., Oct. 2001, available at <http://www.sociology.org/content/vol005.004/th.html> (last visited Aug. 20, 2011).

16. The word “drugs” is used here to encompass FDA oversight of drugs, devices, vaccines and biological.

17. See Yevgenia Shtilman, *Pharmaceutical Drug Testing in the Former Soviet Union: Contract Research Organizations as Broker-Dealers in an Emerging Testing Ground for America’s Big Pharma*, 29 B.C. THIRD WORLD L.J. 425 (2009).

study populations.”¹⁸ Glickman and others estimate that the large pharmaceutical companies conduct between fifty and seventy percent of the initial phases of research, Phase One and Two clinical trials, outside the United States¹⁹ – the practice continues because it is lucrative. As one commentator notes, “[t]oday, the greatest obstacle to ensuring the health and safety of participants in overseas trials may be the lack of regulation over the [independent contractors] employed by Western pharmaceutical manufacturers. Developing, unstable countries are generally ill-equipped to oversee, much less manage, the clinical trials being held within their borders.”²⁰

While there have been some efforts both in the United States and by other countries at bringing the practice of overseas drug testing under some sort of review, they are weakly written and weakly enforced. U.S. laws that require the registering of clinical trials in order for them to form the basis of an application for a drug, device, or biological for sale in the United States are intended to prevent the hiding of bad results, not to protect clinical subjects.²¹ When it comes to protecting subjects, the FDA is clear that it does not demand compliance with U.S. law. The FDA advises applicants that “if the drug is manufactured outside of the U.S. or its territories, the trial sites are all outside of the U.S., and the trial is not being conducted under an [investigational new drug application], then it would not be considered to be subject to section 505 of the [Food, Drug, and Cosmetic] Act or section 351 of the [Public Health Service] Act, and the clinical investigation would not be an ‘applicable drug clinical trial.’”²²

Registry laws are even less able to protect subjects. Research that takes the form of a pilot study, which is never intended for submission to U.S.

18. Overseas Drug Trials Test the System’s Safety, Question Drugs’ Efficacy (Feb. 18, 2009), <http://unchealthcare.wordpress.com/2009/02/18/overseas-drug-trials-test-the-systems-safety-efficacy/>.

19. Seth Glickman et al., *Ethical and Scientific Implications of the Globalizations of Clinical Research*, N. ENGL. J. MED., Feb. 19, 2009, at 816 (estimating that “as of November 2007, approximately one-third of industry-sponsored Phase 3 clinical trials were conducted solely outside the United States, and a majority of study sites (13,521 of 24,206) were located outside the United States”).

20. Shtilman, *supra* note 17, at 436. See also FDB Media, Clinical Research Organization Services by Promedica International, <http://www.fdbnetwork.com/Clinical-Research-Org-CRO>; Biores, Biomedical Research Directory, http://www.biores.org/dir/Companies/Contract_Research_Organizations/.

21. World Health Org., About the WHO ICTRP, <http://www.who.int/ictrp/about/en/>; See generally Carolyne R. Hathaway et al., “The Web of Clinical Trial Registration Obligations: Have Foreign Clinical Trials Been Caught?,” 64 FOOD & DRUG L.J. 261 (2009) (concluding that companies need to comply with many different U.S. and international regulations when conducting a clinical trial overseas).

22. Nat’l. Inst. of Health, Elaboration of Definitions of Responsible Party and Applicable Clinical Trial 8 (Mar. 9, 2009), <http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf>.

regulators, is completely excluded from even these registries. Moreover, the FDA does not require registration of every drug trial. One FDA publication regarding clinical trials for serious and life-threatening diseases notes that HHS, through the NIH, is required by the 1997 FDA Modernization Act to establish “a registry of clinical trials [for both] federally and privately funded trials of experimental treatments for serious or life-threatening diseases.”²³

Many countries with their own active human subject research programs have adopted some laws regulating human subject research that track the principles in the doctrines of Helsinki.²⁴ But even countries that have laws covering harm caused by researchers have difficulty enforcing them. One frequently cited code is the European Union’s guidelines for “Good Clinical Practice” by the International Conference on Harmonization.²⁵ As Shtilman writes, “[b]ecause there is no positive international law mandating CRO compliance with the relevant domestic laws of the clinical studies’ sponsors, the resulting ‘regulatory vacuum’ makes it difficult for these countries to ensure the welfare of trial participants and forces them to rely on foreign data and foreign review processes.”²⁶

There are many other sources of guidelines but all, as their name suggests, are voluntary.²⁷ International organizations such as the European International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the Council for International Organizations of Medical Sciences working with the World Health Organization all have codes of ethical conduct²⁸ and have made attempts to track clinical trials, but their provisions are not enforceable

23. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 113(a)(2). The bare provisions of this statute are still being discussed and interpreted. See Congressional Research Service, *Clinical Trials Reporting and Publication* (July 12, 2007), available at <http://www.fas.org/sgp/crs/misc/RL32832.pdf>; Office of Legislative Pol’y & Analysis, *Access to Clinical Trial Information*, <http://olpa.od.nih.gov/legislation/109/pendinglegislation/fact.asp>; HHS et al., *Guidance for Industry Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* (Mar. 2002), <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126838.pdf>. See also §§ 112-13, 117, 111 Stat. 2296, 2309-12, 2315-16 (1997) (codified at 21 U.S.C. § 356 (2000), 42 U.S.C. § 282 (2000), 21 U.S.C. § 355(i) (2000))

24. New York Univ., *Tutorial Chapter 16: What are researchers’ obligations when doing research in foreign countries?*, <http://www.nyu.edu/ucaih/tutorial/16/>.

25. See International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Efficacy Guidelines*, <http://www.ich.org/products/guidelines/efficacy/article/efficacyguidelines.html>.

26. Shtilman, *supra* note 17, at 436.

27. See Office for Human Research Protections, *International*, <http://www.hhs.gov/ohrp/international/index.html>.

28. See World Health Organization, *Ethical Standards and Procedures for Research with Human Beings*, <http://www.who.int/ethics/research/en/>.

under U.S. law. There is, therefore, a significant legal gap because the FDA does not require a sponsor presenting such an application to prove that their clinical trials were conducted under the same regulations as if they had occurred in the United States. Instead, the company must file Good Clinical Practice, raising concerns about the extent to which the human subjects were provided with informed consent and had adequate protection against injury.

Congress already authorizes the FDA to oversee drug manufacturing plants overseas, but the FDA does not interpret this as an extension to direct oversight of clinical trials.²⁹ What is needed to close the gaps is new legislation that covers research activity within the United States, but also which makes it illegal for U.S. companies to engage in risky human subject research activities outside of the United States. There is no inherent reason why the United States cannot enforce its laws outside of its territorial boundaries.³⁰ In a report discussing the application of criminal law outside the United States, the Congressional Research Service concluded that “[t]he Constitution does not forbid either Congressional or state enactment of laws which apply outside the United States. Nor does it prohibit either the federal government or the states from” applying American law in situation where behavior outside the United States has an effect on events inside the United States.³¹ There are many precedents for the extension of U.S. law, including laws that prohibit bribery of foreign officials,³² tax evasion, trademark abuse,³³ travel for the purpose of engaging in sex with minors,

29. See E. M. Ambler, *Plugging the GATTs and WTOs: Toward a Globalized Pharmaceutical Regulatory Framework*, 29 BIOTECHNOLOGY L. REP. 3 (2010) (arguing that the FDA has the authority to negotiate international agreements and to inspect overseas drug manufacturing plants but has not done so effectively because of lack of enforcement resources and citing 21 U.S.C.A. § 381 which empowers the Secretary of Health and Human Services and, by extension, the FDA to enforce the same regulatory standards on prescription drug imports as on domestically produced prescription drugs); See also FDA Division of Field Investigations, Guide to International Inspections and Travel, § 302.1 (Apr. 30, 2009), <http://www.fda.gov/ICECI/Inspections/ForeignInspections/default.htm> (“The intent of the international inspection program is to ensure that products manufactured in foreign countries meet the same standards of quality, purity, potency, safety, and efficacy as required of domestic manufacturers.”).

30. See *Developments in the Law- Extraterritoriality*, 124 HARV. L. REV., 1226, 1228 (2011) (“[A] state’s extraterritorial application of its law can serve a range of state and non-state interests, and also suggest that extraterritoriality may support the core values of the international order as often as it harms them.”).

31. Charles Doyle, *Extraterritorial Application of American Criminal Law*, Cong. Research Serv. No. 94-166 A (Aug. 11, 2006), available at <http://www.au.af.mil/au/awc/awcgate/crs/94-166.pdf> (last visited Aug. 20, 2011).

32. Foreign Corrupt Practices Act of 1977, 15 U.S.C. §§ 78dd-1 to -3 (2006).

33. Trademark Act of 1946, Pub. L. No. 79-489, 60 Stat. 427 (codified as amended at 15 U.S.C. §§ 1051-127 (1988)).

and deliberate invasion of child labor laws.³⁴ Indeed, the Justice Department recently announced its intent to investigate violations of the Foreign Corrupt Practices Act in relation to the testing of medical devices overseas. This is based on “[a] recent report by the HHS Office of Inspector General [which] noted that eight percent of marketing applications to the FDA in 2008 relied exclusively on foreign data, 80 percent of approved marketing applications for drugs and biologics relied on at least one foreign clinical study, and 78 percent of all human subjects were enrolled at foreign sites.”³⁵

Current efforts at seeking redress for subjects of medical research injured overseas by American corporations are inadequate to address the scope of the problem. For example, although some Nigerians whose children were injured in drug trials conducted in their country by Pfizer were allowed to sue on the Alien Tort Claims Act,³⁶ this is far from comprehensive protection.

III. CONCLUSION

Unfortunately, human subject research is a field where ethics has always outpaced law. Often concerns about practices are realized and discussed long before legislation is passed to address them. This is especially true in the very profitable business of testing drugs for sale in the U.S. market.

The regulations proposed by HHS show great promise in closing one of the serious gaps in oversight by requiring that all research conducted under the auspices of a university or college that receives federal funding comply with the Common Rule. However, since this rule does not extend any regulatory oversight to research by an entity that does not receive federal funding it fails to cover the increasingly large amount of research conducted overseas. Indeed, increasing the regulation of research within the United States may have the perverse effect of making overseas research more attractive. It is well within the authority of the U.S. Congress to extend

34. See generally Mark Gibney, *The Extraterritorial Application of U.S. Law: The Perversion of Democratic Governance, the Reversal of Institutional Roles, and the Imperative of Establishing Normative Principles*, 19 B.C. INT’L & COMP. L. REV. 297 (1996) (tracing development of current doctrine that Congress has the authority to pass laws which require compliance with U.S. law outside the borders of the United States if there is an effect on events inside the United States).

35. Ed Silverman, *Feds Probe Payments in Overseas Drug Trials* (Aug. 9, 2010), <http://www.pharmalot.com/2010/08/feds-probe-payments-in-overseas-drug-trials/>.

36. *Pfizer, Inc. v. Abdullahi*, 130 S.Ct. 3541 (June 29, 2010) (denying certiorari); Joe Stephens, *Pfizer to Pay \$75 Million to Settle Trovan-Testing Suit*, WASH. POST, July 31, 2009 at A15 (explaining that Pfizer has subsequently settled both lawsuits for a reported \$75 million). See also Business & Human Rights Resources Centre, Case profile: Pfizer Lawsuit (re Nigeria), <http://www.business-humanrights.org/Categories/Lawlawsuits/Lawsuitsregulatoryaction/LawsuitsSelectedcases/PfizerlawsuitreNigeria>.

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extraterritorial enforcement of the Common Rule to clinical research done by companies that also do business in the United States. Just as it is illegal to use child labor to make U.S. products in Asia or to bribe officials overseas, it should be illegal to conduct medical research with human subjects who do not have available to them the same protections ensured by basic principles of human dignity.