

**A TAXONOMY FOR ANALYZING LEGAL AND ETHICAL ISSUES ARISING WHEN CONDUCTING HUMAN SUBJECT RESEARCH OUTSIDE THE BORDERS OF ONE’S OWN COUNTRY**

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*The outsourcing of clinical trials to countries where sick people are so poor they are ready to sign up to anything, whether or not they can read what's on the consent form, is now public knowledge.*

– John Le Carré<sup>1</sup>

## I. INTRODUCTION

Every day, all around the world, doctors and scientists are leaving their home countries to conduct medical experiments intended either to increase knowledge or produce a marketable product using as their subjects people living in countries likely to have less infrastructure to protect their interests.<sup>2</sup> Their reasons for doing this vary from altruism to curiosity to profit, but when something goes wrong, when one of these subjects suffers harm, there is no clear path to legal redress. For example, if a team of French researchers go to Lithuania to test a cholesterol drug that they hope to sell in the United States, there could be as many as four different legal systems: that of the country where the research took place, the home country of the researchers, the country where the product will be sold, and

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1. John Le Carré, *Foreword* to SONIA SHAH, *THE BODY HUNTERS: TESTING NEW DRUGS ON THE WORLD'S POOREST PATIENTS*, at viii (2006).

2. See Talea Miller, *'Explosive' Growth in Foreign Drug Testing Raises Ethical Questions*, PBS NEWSHOUR (Aug. 23, 2011), <http://www.pbs.org/newshour/rundown/sending-us-drug-research-overseas> (discussing factors that have shifted clinical trials to developing countries).

any applicable international law or agreement among any of the parties involved.

This article brings together a widely scattered literature outlining the current legal and ethical protections available for human beings who are the subjects of medical research conducted by agents of institutions located in countries other than their own. It builds on an existing taxonomy for evaluating the ethics of different reasons for conducting research outside of one's home country and adds to it a structure for applying legal avenues for redress. It gives particular consideration to U.S. law not because U.S. companies are any more involved in the practice of overseas human testing than pharmaceutical companies based elsewhere, but because the United States is the largest and most profitable market for the products that emerge from these tests. Therefore, a change in the legal requirements for selling a drug in the United States would have considerable global effect.<sup>3</sup> It also highlights a decision made by the Food and Drug Administration to apply a different standard of human subject protection for studies occurring overseas than ones taking place in the United States.

The concerns addressed here do not assume that the United States has the best possible protections for human subjects of research, or even that international standards such as the ICH's Good Clinical Practices are inadequate, rather it is the fact of applying different standards abroad than would be applied at home.

## II. SCOPE OF THE PROBLEM

There is no legal requirement in any country to track, let alone report, human subject research being conducted within its own borders. Equally, there is no requirement to track or report what percentage of that research is being conducted by or on behalf of individuals, institutions, organizations, or entities whose main place of domicile is in a different country. Therefore,

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3. See Jennifer S. Bard, *What to Do When You Can't Hear the Whistleblowing: A Proposal to Protect the Public's Health by Providing Whistleblower Protection for Medical Researchers*, 9 *IND. HEALTH L. REV.* 1, 11, 12, 15-17 (2012) (discussing the increased usage of prescription drugs in the United States).

all attempts at quantification must come from aggregation of unofficial data. For example, in 2008, reporters Donald L. Barlett and James B. Steele did their study of publically available material submitted by drug companies to the FDA and found that 6,485 of the trials took place outside of the United States.<sup>4</sup> Another source of information comes from Wemos, a Dutch nongovernmental organization that seeks to promote clinical trials overseas in order to advance public health in general. As it explains:

[p]ublic health is strongly influenced by the effects of globalization, which range from free trade to climate change to population growth. Many of the health challenges facing us today are not simply domestic issues, but transcend national boundaries, meaning we should no longer be focusing on purely domestic solutions. Many health problems still lack supra-national policy. Tackling those challenges will require effective cooperation, policy and governance at a global level.<sup>5</sup>

However, Wemos has also served as a watchdog and has issued several reports on what it describes as the “Clinical Trials Industry” in Kenya,<sup>6</sup> South Africa,<sup>7</sup> and other non-EU countries.

Another source of information about how much clinical research is being done overseas comes directly from articles and reports within the research community.

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4. Donald L. Barlett & James B. Steele, *Deadly Medicine*, VANITY FAIR (Jan. 1, 2011), <http://www.vanityfair.com/politics/features/2011/01/deadly-medicine-201101>.

5. *Our Work*, WEMOS, [http://www.wemos.nl/Eng/wemos\\_projects.htm](http://www.wemos.nl/Eng/wemos_projects.htm) (last updated May 1, 2014).

6. WEMOS, THE CLINICAL TRIALS INDUSTRY IN KENYA: REALITIES, RISKS AND CHALLENGES, (2014), *available at* [http://www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20Medicijnen/Boekje%20Kenia%20\(1\).pdf](http://www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20Medicijnen/Boekje%20Kenia%20(1).pdf) (last visited Oct. 14, 2014).

7. WEMOS, THE CLINICAL TRIALS INDUSTRY IN SOUTH AFRICA: ETHICS, RULES AND REALITIES (2013), *available at* [http://www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20Medicijnen/Clinical\\_Trials\\_Industry\\_South\\_Africa\\_2013\\_v3.pdf](http://www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20Medicijnen/Clinical_Trials_Industry_South_Africa_2013_v3.pdf) (last visited Oct. 14, 2014).

A. *Why Is Taking Human Subject Research and Clinical Drug Trials Overseas a Problem?*

All of us in the United States assume that the prescription drugs we use have been certified as safe and effective by the Food and Drug Administration. That is correct. But we may also assume that the data the drug companies supply to the FDA comes from clinical trials conducted under the same standards of safety for the human beings involved as would apply in the United States. This is not true.

The FDA does not test drugs itself. Instead, it relies on data supplied by the companies seeking to sell them.<sup>8</sup> When clinical drug trials are conducted in the United States, the FDA requires that the companies follow U.S. laws passed to protect human subjects of research.<sup>9</sup> But when the trials are conducted exclusively outside of the United States, the FDA does not require sponsors to apply for an IND.<sup>10</sup> At one point, there was confusion as to whether sponsors who did not need an IND had to comply with 21 C.F.R. 312 anyway. This was clarified on April 28, 2008 when the FDA issued a final rule modifying 21 C.F.R. 312.120, entitled “Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application.”<sup>11</sup>

Before the 2008 modification, 21 C.F.R. 312 required that studies conform to whichever of the following provides greater

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8. *How Drugs are Developed and Approved*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm> (last updated Nov. 10, 2014).

9. They do this by requiring that sponsors intending to test an unapproved drug or device in the United States to obtain an Investigational New Drug (IND) or Investigational Device Exemption (IDE), which then binds the Sponsor to all FDA informed consent and institutional review board requirements. *See* Investigational New Drug Application, 21 C.F.R. § 312.20 (2014) (discussing the FDA requirements for an IND); *see also* Investigational Device Exemptions, 21 C.F.R. § 812 (2014) (discussing the FDA requirements for an IDE). *See generally* *Acceptance of Foreign Clinical Studies: Information Sheet*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126426.htm> (last updated June 25, 2014).

10. Bard, *supra* note 3, at 30–32.

11. Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 73 Fed. Reg. 22800 (Apr. 28, 2008) (codified as 21 C.F.R. pt. 312).

protection of the human subjects: (1) the ethical principles contained in the 1983 version of the Declaration of Helsinki; or (2) the laws and regulations of the country in which the research was conducted.<sup>12</sup>

Also, under 21 CFR 814.15(a) and (b), the FDA will accept a foreign clinical study involving a medical device not conducted under an IDE only if the study conforms to whichever of the following provides greater protection of the human subjects: (1) the ethical principles contained in the 1983 version of the Declaration of Helsinki; or (2) the laws and regulations of the country in which the research was conducted.<sup>13</sup>

This reference to the “Declaration of Helsinki” refers to a statement by the World Medical Association (WMA) of “Ethical Principles for Medical Research Involving Human Subjects.”<sup>14</sup> The first Declaration of Helsinki was adopted by the WMA in 1964 and has been revised nine times since then, with the most recent version adopted at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.<sup>15</sup> Therefore, the FDA’s reference to the 1983 version of the Declaration of Helsinki refers to a version that has been edited and superseded eight times.<sup>16</sup>

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12. Foreign Clinical Studies not Conducted Under an IND, 21 C.F.R. § 312.120 (2001) (amended 2008).

13. Premarket Approval of Medical Devices, 21 C.F.R. § 814.15(a), (b) (2014).

14. WMA *Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects*, WORLD MED. ASS’N, <http://www.wma.net/en/30publications/10policies/b3/> [hereinafter *Declaration of Helsinki*] (last visited Nov. 14, 2014).

15. *Id.* See generally 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, 450 (2009) (“The Declaration of Helsinki is less trial participant-focused than the Nuremburg Code and is regarded by some as the definitive statement of medical ethics regarding medical research, is part because it was signed by the United States and incorporated into the FDA’s regulations for overseas clinical research in 1975.”)

16. See Tibor Szentendrei, *Better Protection for Those Helping Medical Research: Declaration of Helsinki Revised*, ALTARUM INST. (Mar. 20, 2014), <http://altarum.org/health-policy-blog/better-protection-for-those-helping-medical-research-declaration-of-helsinki-revised>, for a comparison of the 1983 and current versions and information about the FDA’s rejection of the 2000 version of the Helsinki Declaration, which limited the use of placebos. See also John A. Lewis et al., *Placebo-Controlled Trials and the Declaration of Helsinki*, 359 LANCET 1337, 1338–39 (2002) (noting that “[a] strict interpretation of the [2000 revision of the] declaration seems to rule out clinical trials that use a placebo control group whenever licensed therapeutic methods already exist,

Critics of the FDA's decision not to require sponsors of drugs tested overseas to comply either with the latest version of the Helsinki Doctrine or the regulatory requirements of an IND argue that as a result the protection of human subjects overseas is inadequate.<sup>17</sup> Specifically, clinical trials overseas are allowed to use placebos even when there is an existing effective treatment. This is only permissible in the United States when there is no effective treatment. Others minimize the concerns stating that, in effect, the FDA is complying with international standards in that many countries where drugs are tested follow the guidance of the International Conference on Harmonization - Joint Safety/Efficacy.<sup>18</sup> As a legal matter, the FDA's decision has created the need to analyze the laws of the country where the drug is tested in order to compare it to the Helsinki "ethical principles." This is a "comparing apples to oranges" task because of the inherent differences in a legal system and principles of ethics.

The volume of human subject research conducted overseas has created the need for a way of first categorizing the legal and ethical issues arising when human subject research is conducted overseas and then identifying the sources of law, and ethics, that can be used to analyze specific situations. This article addresses this need by creating a taxonomy that will assist in identifying the legal issues arising in a specific scenario and then identifying the sources of law available for protecting the people who are the subject of these clinical trials. In so doing, it adds a legal perspective to a substantial ethical literature.<sup>19</sup>

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preferring active controls"); *cf. Declaration of Helsinki, supra* note 14 (showing that the Declaration of Helsinki, as amended, endorsed using placebos).

17. See Fiona Fleck, *Clinical Trials Without Ethical Review*, 10 IAPAC MONTHLY 228, 228 (2004) (discussing inadequate laws in developing countries for clinical trials).

18. See James R. Dixon, *The International Conference on Harmonization: Good Clinical Practice Guideline*, 6 QUALITY ASSURANCE 65 (1999) (discussing the ICH's adoption of good clinical practices). See *History*, INT'L CONF. ON HARMONIZATION, <http://www.ich.org/about/history.html> (last visited Nov. 14, 2014), for a discussion of the history of the ICH.

19. See Jacob Schuman, *Beyond Nuremberg: A Critique of Informed Consent in Third World Human Subject Research*, 25 J.L. & HEALTH 123, 136-37 (2012) (discussing proposals to enforce the informed consent ethical standard in the Third World through legal mechanisms).

*B. Why Are Companies Taking Human Subject Research Overseas?*

The practice of pharmaceutical companies testing their products on human beings living in countries other than the countries where the company is either registered or uses as its primary base of operations is a widespread and global phenomenon.<sup>20</sup> As this article reviews, there are many reasons that this occurs. In many ways it is analogous to the wholesale transfer of product manufacturing to China. Whether the product is sneakers, iPhones, cars, or pharmaceuticals, companies find it cheaper and easier to contract with or set up factories in locations far from home.

Yet as serious an issue this is for workers, and to some extent consumers, the practice of not just manufacturing but actually testing drugs on people who live in countries with less rigorous health and safety regulations adds another layer of intensity to the human rights concerns. The individuals involved are either already sick and therefore even more vulnerable than workers driven to low-paying jobs because of poverty, or are risking their bodily integrity.

Another reason why overseas testing is attractive is that it is easier for companies to iron out problems that arise without having to disclose them.<sup>21</sup> This problem is not unique to trials that occur overseas. The FDA has been trying, without great success, to require companies to disclose the result of all clinical trials, whether they are used to support an application for approval of a new product or not.<sup>22</sup>

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20. See Miller, *supra* note 2 (explaining that trials conducted in foreign countries have increased in the past few years).

21. See Barlett & Steele, *supra* note 4 (noting the FDA's minimal monitoring of foreign clinical trials).

22. Ed Silverman, *What Clinical Trials? Many Study Results Remain Under Wraps*, WALL ST. J. (July 22, 2014, 2:55 PM), <http://blogs.wsj.com/pharmalot/2014/07/22/what-clinical-trials-many-study-results-remain-under-wraps>.

### C. *Where Do the Trials Occur?*

There is a fluctuation between which countries are the most popular for exporting clinical trials.<sup>23</sup> This can be a reflection of the local economy or political situation; it is fair to imagine that the current war in the Ukraine is making it a less attractive option. Another factor is, as in India, a decision by the host country that participating in clinical trials is not in its country's best interests.<sup>24</sup> The current hot spot for overseas clinical trials is China.<sup>25</sup> Latin America is also a popular location.<sup>26</sup>

### D. *Who Conducts Human Subject Research Overseas?*

Most of the information about overseas testing is about the activities of drug companies developing new products because that activity is the most conspicuous. Most pharmaceutical companies are publically traded and must make regular reports to their shareholders as well as to the regulatory agencies in the countries where they do business.<sup>27</sup> However, there are many other groups conducting human subject research overseas about which we have much less information, and there is a considerable amount of pharmaceutical company research that is never disclosed outside the country.

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23. See Tomas Novak et al., *Decline of Clinical Trials in Central and Eastern Europe: Fluctuation or Trend?*, APPLIED CLINICAL TRIALS (June 16, 2014), <http://www.appliedclinicaltrials.com/appliedclinicaltrials/article/articleDetail.jsp?id=846044> (analyzing statistical data to show the relative change in the number of clinical trials in different regions).

24. See Amy Kazmin & Andrew Jack, *India Ruling on Drug Trials Injects Fears for Industry's Health*, FIN. TIMES (Nov. 18, 2013), <http://www.ft.com/intl/cms/s/0/76335e22-4d03-11e3-9f40-00144feabdc0.html#axzz3M2fGkLZN> (discussing India passing tough rules in response to clinical trials conducted in India).

25. Diana L. Anderson, *BRIC and Mortar: Clinical Trial Growth in Latin America, Eastern Europe and Asia*, 3 J. FOR CLINICAL STUDIES 22, 27 (2011).

26. See *id.* at 22 (discussing Brazil's strengths as a clinical research center).

27. See Kathleen M. Boozang, *Responsible Corporate Officer Doctrine: When Is Falling Down on the Job a Crime?*, 6 ST. LOUIS U. J. HEALTH L. & POL'Y 77, 99 (2012) (stating it is rare for a pharmaceutical company to not be publically traded). See generally *Pharmaceuticals: Regulatory Agencies*, GLOBAL EDGE, <http://globaledge.msu.edu/industries/pharmaceuticals/regulatory-agencies> (last visited Oct. 3, 2014) (providing a list of several countries' regulatory agencies).

A growing force in overseas medical research consists of private foundations, such as those operated by Bill & Melinda Gates and Michael J. Fox's private foundation that studies and develops treatments for Parkinson's disease.

The practice of testing biologics, drugs, and devices outside the home country of the companies developing them or the countries where they will be sold is so widespread that an industry has developed to facilitate the process. A review of the promotional materials these companies make available to pharmaceutical companies gives a clear picture of why this is so attractive.<sup>28</sup> The shifting of trials to Eastern Europe appears to be highly motivated by cost.<sup>29</sup> The following overview from a company that markets strategic advice to pharmaceutical companies lays out the advantages directly:

[T]he population of Central and Eastern European countries exceeds that of either the United States or the five largest Western European markets combined. Furthermore, there is a lower saturation of competing trials within the region compared to other, more developed markets.

Besides a large patient population Central and Eastern Europe offer the drug and device industries a convenient location—especially for European-based countries—to conduct clinical studies. The region has a long history of clinical development, making it easier to find and train skilled investigators.<sup>30</sup>

However, here too, possible human rights problems emerge, as one of the benefits is described as “treatment-naïve” patients.<sup>31</sup> This is another way of saying that people have less access to industrialized standards of medical care. This can make it easier to determine the effects of the drug being tested because the patients have not been treated before. However, it

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28. Novak et al., *supra* note 23.

29. *Id.* at 1.

30. *Emerging Markets Clinical Trials: Eastern Europe (PH145)*, CUTTING EDGE INFO., <http://www.cuttingedgeinfo.com/research/clinical-development/central-eastern-europe-trials> (last visited Oct. 26, 2014).

31. *See id.* (explaining that the access to treatment-naïve patients in Central and Eastern Europe makes it an ideal location to host clinical trials).

also makes the patients more eager to participate because it is their only opportunity for potentially life-saving, or certainly life-enhancing, care.<sup>32</sup> As another company touting Eastern Europe as a cost-effective destination explains, Eastern Europe has a proven track record and is known for “very good patient compliance” and “fast recruitment.”<sup>33</sup>

Although the testing done by pharmaceutical companies with the intent of developing a marketable product is the most visible and probably the largest problem in need of regulation, an effective legal taxonomy must also include other scenarios in which human subjects are involved. These include research studies conducted to advance knowledge, studies by private foundations to test products that they, themselves do not intend to market, and governments going overseas to preemptively study conditions before they become a threat.

### III. ETHICAL ISSUES IN INTERNATIONAL COLLABORATIVE RESEARCH

Human Subject Research is a field shared by scientists, health care providers, ethicists, and lawyers. It is common for ideas and proposals to develop in the literature of one field that do not reach the awareness of those working outside of it. So, for example, a 2001 report issued by the National Bioethics Advisory Committee titled “Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries” began its review of clinical design by noting that

[i]t may be useful to classify international collaborative research projects in developed and developing countries on a continuum. At one end of the continuum is research that has no practical relevance to the health needs of the host country, but is important to the foreign sponsor or researcher. At the other end of the spectrum is research that is directly relevant to the health concerns of the host country, but not to sponsors or researchers.<sup>34</sup>

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32. *Region*, ECRON ACUNOVA, <http://www.ecronacunova.com/experience/region.htm> (last visited Oct. 3, 2014).

33. *Id.*

34. NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN

The community of those concerned about ethical issues arising from human subject research has long been concerned with the particular problems that arise when human subject research takes place outside of the researcher's own home country.<sup>35</sup>

*A. Lack of Access to Product by Country Where It Is Tested*

Declaring that Africans should not continue to be used as "guinea pigs" for foreign pharmaceutical companies, Zimbabwe's Health and Child Care Minister Dr. David Parirenyatwa explained that "[w]hen these drugs are proved to work, they are sold back to Africa very expensive [sic], yet the trials would have been conducted on our people."<sup>36</sup> He also called for new laws creating a more just distribution of drugs tested in African countries.<sup>37</sup>

The question of this article is to develop a framework for analyzing how the law, defined in very broad terms, can be used to address the human rights concerns raised by current practices.

*B. Quality Issues*

As many ethical issues as there are with conducting human subject research overseas, there are also considerable concerns about the quality of that research.<sup>38</sup> Framing the issue in their *Vanity Fair* article titled "Deadly Medicine," Barlett and Steele wrote:

Prescription drugs kill some 200,000 Americans every year. Will that number go up, now that most clinical trials are conducted overseas—on sick Russians, homeless Poles, and slum-dwelling Chinese—in places where regulation is virtually nonexistent, the F.D.A.

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INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES 19 (2001), available at <https://bioethicsarchive.georgetown.edu/nbac/clinical/Vol1.pdf>.

35. *Id.* at 1.

36. Paidamoyo Chipunza, *Parirenyatwa Speaks on Drug Trials*, HERALD (Apr. 30, 2014), <http://www.herald.co.zw/parirenyatwa-speaks-on-drug-trials>.

37. *Id.*

38. See Barlett & Steele, *supra* note 4 (explaining that some medical researchers question whether tests done in other countries are relevant to Americans).

doesn't reach, and "mistakes" can end up in pauper's graves?<sup>39</sup>

#### IV. TAXONOMY OF THE REASONS FOR LEAVING THE HOME COUNTRY

The first question to ask in analyzing the legal and ethical concerns raised by conducting human subject research outside the borders of one's own country is the researcher's reason for being there. This article identifies three primary categories of research conducted overseas: research related to a condition specifically in that country, research brought overseas for cost control or the convenience of the researchers, and research brought overseas to evade the human subject protections of the home country.

##### *A. Is There a Substantive Issue Directly Related to the Research that Requires It Being Done in Another Country?*

As of the writing of this article, an Ebola epidemic is sweeping through Africa. A disease with a near 90% mortality rate, there is no widely available treatment beyond IV fluid support and no known preventative other than sanitation.<sup>40</sup> Victims die of Ebola so quickly that so far, it has not spread far beyond Africa—so any effective study of the disease or development of an intervention must take place where and when an outbreak occurs.<sup>41</sup> Yet even when the reason for travel is sound and the motive altruistic, the potential for abuse is real. An Ebola drug trial taking place in a U.S. hospital would be carefully monitored to ensure voluntary participation and fair distribution of the intervention. Yet, even in that situation, it is

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39. *Id.*

40. *Critical Supplies Reaching Health Workers Fighting Ebola Outbreak*, RELIEFWEB (Sept. 3, 2014), <http://reliefweb.int/report/liberia/critical-supplies-reaching-health-workers-fighting-ebola-outbreak>; *Ebola Virus Disease Fact Sheet*, HIGH COMMISSION OF INDIA IN NIGERIA, <http://www.indianhcabuja.com/docs/Ebola%20Fact%20Sheet.pdf> (last visited Sept. 13, 2014).

41. Sarah Boseley, *Ebola Rages in Africa as West Agonises Over Ethics of Vaccine and Drug Testing*, GUARDIAN (July 31, 2014), <http://www.theguardian.com/society/2014/jul/31/ebola-africa-west-ethics-vaccine-drug-testing>.

still possible to apply the metric that would be used in the home country.

A researcher from Europe studying Nile River Blindness needs to go to Egypt. A researcher studying sex workers in Thailand needs to go to Thailand. Deadly epidemics and chronic disease are now, always have been, and very likely always will be a universal feature of human existence on Earth. Yet unlike as recently as a few hundred years ago, the ability to prevent sickness and treat those afflicted by it is by no means equally distributed among those living on our planet today. Large segments of the global population lack access to clean water and protection from vectors like mosquitoes and rats, let alone the effective vaccines and drugs available in wealthy industrial countries.<sup>42</sup>

While development of drugs that will only be of interest to resource-poor countries may not be a top priority of pharmaceutical companies that have to answer to their shareholders, there are entities devoted to the task. One of the most prominent is the Drugs for Neglected Diseases Initiative.<sup>43</sup> Moreover, even when the motivation of researchers is not solely profit, there are still considerable disagreements on both ethical and efficacy grounds, surrounding this kind of study.<sup>44</sup>

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42. See *Water, Sanitation and Hygiene: Introduction*, UNITED NATIONS CHILDREN'S FUND, <http://www.unicef.org/wash> (last visited Sept. 5, 2014) (explaining that 768 million people use unsafe drinking water); see also *World Immunization Week: 24–30 Apr. 2014*, WORLD HEALTH ORG., <http://www.who.int/campaigns/immunization-week/2014/event/en> (last visited Sept. 5, 2014) (highlighting that “[i]n 2012, an estimated 22.6 million infants were not reached with routine immunization services”).

43. See *New Oral Drug Candidate for African Sleeping Sickness*, DRUGS FOR NEGLECTED DISEASES INITIATIVE (Dec. 6, 2012), <http://www.dndi.org/media-centre/press-releases/1505-new-oral-drug-candidate-hat.html> (“The Drugs for Neglected Diseases initiative (DNDi) is a not-for-profit research and development organization working to deliver new treatments for neglected diseases.”).

44. See SONIA SHAH, *THE BODY HUNTERS: TESTING NEW DRUGS ON THE WORLD'S POOREST PATIENTS* 95 (2006) (describing how researchers defending a controversial AIDS study justified not using the best standard of care available in the world by arguing that they only had to provide the highest standard of care available in the foreign country).

*B. Is the Research Being Conducted Overseas to Lower Costs or for the Convenience of the Researchers?*

It is neither inherently unethical nor illegal for a company to reduce the costs of its production. An example of this would be a clinical trial of a new blood pressure medicine tested in a clinical-trial facility in Eastern Europe or in India. Timing is important to pharmaceutical companies because the faster they can get a drug on the market, the longer they have exclusive rights to the profits through patent law. Companies complain of regulatory schemes that, although not directly targeted at clinical trials, still add expense and delay.<sup>45</sup>

*C. Is the Research Being Conducted Overseas to Evade Human Subject Protections of the Home Country or Because It Is Unlikely that Potential Subjects in the Home Country Would Agree to Participate?*

Providing and documenting human subject protection measures add to the administrative burden of conducting research. A decision to leave the country in order to evade these measures does not necessarily mean intent to put a subject at greater risk of physical, mental, or economic harm than would be allowed in the home country. Unfortunately, there are many documented cases where the reason for leaving the United States was because the research either would be illegal or would not be approved on ethical grounds by an institutional review board in the United States.<sup>46</sup>

Journalist and public health advocate Sonia Shah gives one such example, describing a macular degeneration study that required injecting either an experimental drug or a placebo

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45. See Lynne Taylor, *EU Data Plans 'Could Make Cancer Research Impossible'*, PHARMATIMES DIGITAL (July 27, 2014), [http://www.pharmatimes.com/Article/14-07-27/EU\\_data\\_plans\\_could\\_make\\_cancer\\_research\\_impossible.aspx](http://www.pharmatimes.com/Article/14-07-27/EU_data_plans_could_make_cancer_research_impossible.aspx) (explaining how the proposed European Union General Data Protection Regulation will add significant delays that could make cancer research impossible).

46. See William DuBois, Note, *New Drug Research, The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT'L L. 161, 168–69 (2003) (discussing clinical trials performed overseas that would be unethical in the United States).

directly into the patient's eye.<sup>47</sup> Because "there were already many other drugs available" for patients that did not require eye injections, few subjects agreed to participate.<sup>48</sup>

Both categories one and two present issues of potential exploitation of human subjects and the communities where they reside. Yet, it is the third category, research that is specifically taken overseas either to avoid human safety regulations or to take advantage of poverty and lack of access to high quality medical care, that makes potential research subjects more willing to participate than residents of the countries where the products are most likely to be used that causes the most concern.

1. *Studies that Would Be Unattractive to Volunteers in the Home Country*

It is easy to find information about clinical trials taken overseas not to evade ethical rules, but rather to access a more needy and more willing-to-participate population. The extensive literature describing to researchers the advantages of going overseas can be quite direct about the ability to get subjects who would not volunteer to participate in countries where they had other options for getting care.<sup>49</sup> Describing the difficulty of complying with new European Union regulations requiring "pharmaceutical companies to undertake clinical trials within the paediatric population," a piece was written on behalf of a company offering its services in facilitating research in "non-European" countries.<sup>50</sup> The authors first note that

[g]enerally, it is known that there are difficulties associated with the undertaking of paediatric clinical trials, and particularly so in Western Europe. These

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47. SHAH, *supra* note 44, at 5.

48. *Id.*

49. See, e.g., *Geographical Coverage*, ACCELL CLINICAL RESEARCH, <http://www.accelclinical.com/?q=node/4> (last visited October 5, 2014) (discussing the potential to "recruit up to 10 times faster than in the United States" due to the Eastern European healthcare system).

50. Greer Deal & Nikolai Nikitin, *European and Non-European Paediatric Clinical Trials*, REG. REP., May 2009, at 4, 4, available at <http://drupal.topra.org/sites/default/files/regrapart/1/1714/focus1.pdf>.

difficulties relate to ethical, technical and logistical considerations. Many physicians are reluctant to recruit children into clinical trials because they are seen as vulnerable subjects.<sup>51</sup>

In contrast, the authors offer “countries of the former Soviet Union” as locations “where paediatric trials are not associated with severe recruitment problems.”<sup>52</sup> The authors are quick to assure that “[c]linical research in Russia and Ukraine is conducted with strict adherence to GCP principles . . . [which] are strictly monitored by the national authorities.”<sup>53</sup> But it is easier to recruit children into drug trials because “[f]or many parents, the participation of their children in clinical trials means that these children can gain access to free, high-quality medical care, provided by the best specialist centres.”<sup>54</sup>

## 2. *Studies that Would Be Illegal in the Home Country*

But what of human subject trials taken overseas because they involve a level of risk not acceptable in the home country?

Discussions regarding the ethics of clinical drug trials conducted overseas draw strong feelings and often-conflicting worldviews. Drug companies often argue that they are doing a service to populations who would otherwise not have access to care.<sup>55</sup> On the other hand, critics point out that with issues of human rights, an activity or practice that is legal in its home country does not mean that it is acceptable to go to a country where such behavior is both illegal and wrong to engage in it. This debate extends across a variety of topics, but there is a considerable literature focused directly on the practice of overseas human subject research.

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51. *Id.*

52. *Id.*

53. *Id.* at 5.

54. *Id.* at 4.

55. See SHAH, *supra* note 44, at 95 (describing how researchers defending a controversial AIDS study justified not using the best standard of care available in the world by arguing that they only had to provide the highest standard of care available in the foreign country).

One of the best-known and most-documented cases involves Pfizer's trial of the antibiotic Trovan in Nigeria.<sup>56</sup> Trovan was not approved for pediatric use in the United States because it had a high risk of seizure and was no more effective than other widely available and safer antibiotics.<sup>57</sup> Moreover, these alternatives came in formulations that required refrigeration. Trovan did not. When a meningitis epidemic broke out in Africa, Pfizer made Trovan available in remote locations without access to refrigeration, but did not inform parents of the risk that came with this medication. Parents were not given the option of, for example, moving their child closer to a source of refrigeration. Outraged, the parents of children who died sued Pfizer and its executives.<sup>58</sup> Pfizer's defense was that it had complied with all relevant laws because, "[b]efore conducting the Trovan clinical study in Kano, Pfizer sought and obtained all necessary approvals from relevant federal and state government agencies in Nigeria."<sup>59</sup> After having the case dismissed multiple times by the United States District Court for the Southern District New York, the parents eventually settled.<sup>60</sup> The FDA reported that

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56. See DuBois, *supra* note 46, at 164–65 (discussing investigations of Trovan clinical studies, a lawsuit against Pfizer, and an FDA criminal inquiry into Trovan).

57. See SHAH, *supra* note 44, at 146 (discussing why Trovan was not approved for pediatrics).

58. *Id.*

59. PFIZER, SUMMARY: TROVAN, KANO, STATE CIVIL CASE—STATEMENT OF DEFENSE (2007), available at [http://www.pfizer.com/files/news/trovan\\_statement\\_defense\\_summary.pdf](http://www.pfizer.com/files/news/trovan_statement_defense_summary.pdf).

60. Sarah A. Altschuller, *Alien Tort Statute Update: Pfizer Settles Suit with Nigerian Plaintiffs*, CORP. SOCIAL RESP. & THE LAW (Feb. 28, 2011), <http://www.csrandthelaw.com/2011/02/28/alien-tort-statute-update-pfizer-settles-suit-with-nigerian-plaintiffs>. Although Trovan is still on the market, it carries the following "black box" warning: "THE SAFETY AND EFFECTIVENESS OF TROVAFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS LESS THAN 18 YEARS OF AGE, PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED." *Drug Label Information*, DAILYMED, <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=da9b26bb-d2d7-4113-a0f9-c6c2280f4875> (last updated Feb. 2006). The FDA has also issued a warning to consumers not to purchase Trovan over the Internet. *FDA Consumer Safety Alert: Don't Buy These Drugs Over the Internet or From Foreign Sources*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/buyingmedicinesovertheinternet/ucm202893.htm> (last updated Mar. 9, 2010) ("The drugs on this list have important benefits, but they also have serious known risks. As a result, they are available in the U.S. only under

Pfizer had “voluntarily agreed” that use of Trovan would be restricted to only the sickest adults in in-patient facilities.<sup>61</sup>

Another oft-cited study was funded by the National Institutes of Health to test a new method of preventing the transmission of AIDS from pregnant women to their unborn children. By 1997, researchers had developed an almost 100% effective protocol, or schedule, for preventing HIV transmission by giving pregnant women large doses of AZT throughout the course of their pregnancy.<sup>62</sup> It had become the standard of care in the United States and had reduced transmission of HIV in treated women to almost zero.<sup>63</sup> However, it was expensive and time-consuming.<sup>64</sup> It also required considerable cooperation on the part of the mother.<sup>65</sup>

A researcher at Johns Hopkins believed it would be possible to achieve the same results with one large dose of a specific anti-retroviral that had fallen into disuse.<sup>66</sup> There were two problems. First, it was not in the interest of any drug company to develop a protocol that involved using less of their drug. Second, no doctor in the United States would agree to deprive her patients of an effective treatment in order to test one that had no benefits other than reduced costs.

The Johns Hopkins team went to Uganda, where women had no access to AZT and the rate of HIV transmission was very high.<sup>67</sup> They developed a study in which some women

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pecially created safety controls.”).

61. Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Research, U.S. Food & Drug Admin., to Sidney M. Wolfe et al., Pub. Citizen’s Health Research Grp. (Jan. 6, 2000), *available at* <http://www.fda.gov/ohrms/dockets/dailys/00/feb00/021000/pdn001.pdf> (“The Agency and Pfizer have also agreed to a program that will limit the distribution of Trovan to in-patient health care facilities (hospitals and long-term nursing care facilities). In addition, Pfizer is voluntarily recalling Trovan from pharmacies that do not serve in-patient health care facilities.”).

62. SHAH, *supra* note 44, at 80.

63. *Id.* at 80–81.

64. *Id.* at 80.

65. *See id.* (requiring AZT to be administered to infected pregnant women “five times a day . . . for months before delivery,” during delivery by IV infusion, and to the baby “every six hours during its first six weeks of life”).

66. *Id.* at 86.

67. SHAH, *supra* note 44, at 87.

were randomly given the one-time dose and others were given a placebo.<sup>68</sup> They quickly discovered that the one-time dose worked better than not only the placebo, but also the multi-dose regime used in the United States.<sup>69</sup> The study was promptly criticized as being highly unethical.<sup>70</sup> Notably, the *New England Journal of Medicine* published an editorial stating that the study violated the Declaration of Helsinki because it denied research subjects the best available standard of care.<sup>71</sup>

Another example includes the “Golden Rice” study conducted by Tufts University in Boston to study the effects of genetically engineered rice on elementary school children in China.<sup>72</sup>

## V. OPTIONS FOR LEGAL REGULATION OF HUMAN SUBJECT RESEARCH

From a regulatory perspective, there are four sources of law that could apply to any specific human-subject research project.

### A. *Law of the Country Where the Research Takes Place*

The first source of law to consider is that of the country where the research takes place. Almost every country in which human subject research takes place or clinical trials are conducted has some sort of legal regulation.<sup>73</sup> The effectiveness of laws in the country where the research takes place depends on how they can be enforced against a company or individuals when they go home.<sup>74</sup> The enforceability of a judgment or even

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68. *Id.*

69. *See id.* at 98 (stating that only 7 percent of the single-dose nevirapine babies contracted HIV compared with 36 percent in the placebo group and 20 percent of the ultra-short multi-dose AZT babies).

70. *Id.* at 92.

71. *Id.*

72. Anne-Marie Duguet et al., *Ethics in Research with Vulnerable Populations and Emerging Countries: The Golden Rice Case*, 38 N.C. J. INT'L L. & COM. REG. 979, 980 (2013).

73. *See* OFFICE FOR HUMAN RESEARCH PROTS., U.S. DEPT OF HEALTH & HUMAN SERVS., INTERNATIONAL COMPILATION OF HUMAN RESEARCH STANDARDS 3 (2014), <http://www.hhs.gov/ohrp/international/intlcompilation/2014intlcomp.pdf.pdf> (providing links to guidelines from 107 countries that govern human subject research).

74. *See* Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J.

criminal conviction from one country to another is a matter of individual treaty.<sup>75</sup> In other words, the two countries must agree in advance on the conditions under which they would extradite an individual or enforce a judgment.

The Nigerian Trovan litigation<sup>76</sup> provides a prime example of this. Although Pfizer and individual executives were arrested to face criminal charges in conjunction with the eleven children who died after being administered Trovan, the charges were eventually dropped.<sup>77</sup>

The United States, as a matter of general principle, does not assert jurisdiction over acts that occur outside of its own borders.<sup>78</sup> However, Congress has passed several laws that do regulate specific activity. These include the Foreign Corrupt Practices Act<sup>79</sup> and laws intended to prevent sex trafficking.<sup>80</sup>

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INT'L L. 513, 531–33 (2002) (discussing the ineffectiveness of a regional protection agreement due to the inability to apply it extraterritorially).

75. Ralf Michaels, *Recognition and Enforcement of Foreign Judgments*, in MAX PLANCK ENCYCLOPEDIA OF PUBLIC INT'L LAW (Mar. 2009), [http://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=2699&context=faculty\\_scholarship](http://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=2699&context=faculty_scholarship).

76. See *supra* Part IV.C.2.

77. Mike Oboh, *Pfizer Exec Gets Bail in Nigeria Trial over Drug*, WASH. POST (Mar. 4, 2008), <http://www.washingtonpost.com/wp-dyn/content/article/2008/03/04/AR2008030401199.html>; Joe Stephens, *Pfizer Faces Criminal Charges in Nigeria*, WASH. POST (May 30, 2007), <http://www.washingtonpost.com/wp-dyn/content/article/2007/05/29/AR2007052902107.html>. *The Atlantic* magazine suggests that based on information from diplomatic cables released by WikiLeaks, “the world’s largest drugmaker may have blackmailed the head of Nigeria’s Ministry of Justice into dropping a \$6 billion criminal lawsuit.” Walter Armstrong, *Did Pfizer Bribe its Way Out of Criminal Charges in Nigeria?*, ATLANTIC (Dec. 27, 2010), <http://www.theatlantic.com/international/archive/2010/12/did-pfizer-bribe-its-way-out-of-criminal-charges-in-nigeria/68495>.

78. See William S. Dodge, *Understanding the Presumption Against Extraterritoriality*, 16 BERKELEY J. INT'L L. 85, 86–88 (1998) (discussing the Supreme Court’s reluctance to abandon the presumption against extraterritoriality). *But see* Alien Torts Statute, 28 U.S.C. § 1350 (2012) (“The district courts shall have original jurisdiction of any civil action by an alien for a tort only, committed in violation of the law of nations or a treaty of the United States.”).

79. 15 U.S.C. §§ 78m, 78o, 78dd-1–3 (2012); see also Charles F. Smith & Brittany D. Parling, “American Imperialism”: A Practitioner’s Experience with Extraterritorial Enforcement of the FCPA, 2012 U. CHI. LEGAL F. 237, 238–39 (stating that foreign corporations may be subject to U.S. law under the FCPA).

80. Trafficking Victims Protection Act (TVPA), 22 U.S.C. §§ 7101–7112 (2012); 8 C.F.R. § 214.11 (2014).

Another category of laws has the effect of regulating conduct outside of the jurisdiction by imposing requirements on goods imported into the United States.<sup>81</sup> So, for example, by requiring that companies certify that they do not use child labor, the United States essentially applies its own standards against child labor to countries where it may be legal. Another example of this would be the prohibition on importing ivory.<sup>82</sup>

There are two primary ways of applying a country's laws outside of its borders. One is through a "boomerang" statute in which the law of the country where the research takes place stipulates that foreign countries will be subject to the laws of their home countries. The second is a direct assertion by a country of the extraterritorial application of its laws on the actions of its nationals outside of the country.

### 1. *Boomerang Statutes*

Many Latin American countries have adopted a strategy for discouraging companies to take advantage of differences between their home country's laws and the laws of the countries where they do business by adopting "boomerang" statutes that as a matter of "choice of law" apply the home country's laws rather than those of the country where the act took place.<sup>83</sup> A true "boomerang"-type criterion would require the formation of an institutional review board to be asked the question, "Would this study be legal in the United States?"

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81. See, e.g., 19 U.S.C. § 1307 (2012) (prohibiting import of goods produced by forced labor).

82. See *USFWS Moves to Ban Commercial Elephant Ivory Trade: Questions & Answers*, U.S. FISH & WILDLIFE SERV., <http://www.fws.gov/international/travel-and-trade/ivory-ban-questions-and-answers.html> (last visited Nov. 1, 2014) (providing an overview of U.S. law related to elephant ivory).

83. M. Ryan Casey & Barrett Ristroph, *Boomerang Litigation: How Convenient is Forum Non Conveniens in Transnational Litigation?*, 4 *BYU INT'L L. & MGMT. REV.* 21, 27 (2007) (discussing Latin American jurisdictions using "blocking statutes" to force U.S. courts to retain jurisdiction of suits against transnational corporations); see also Cortelyou Kenney, *Disaster in the Amazon: Dodging "Boomerang Suits" in Transnational Human Rights Litigation*, 97 *CALIF. L. REV.* 857, 890–91 (2009) (discussing the prevention of forum shopping by transnational corporations that use *forum non conveniens* to avoid U.S. litigation).

*B. Law of the Country Where the Research or Company Is Based*

Most countries, and almost all countries in which pharmaceutical companies are located, regulate human subject research within their own borders.<sup>84</sup> But the extent to which they claim jurisdiction over the acts of a company that occur outside of the home territory varies considerably.

There are many examples of countries holding their nationals to home-based standards of conduct even when the activity takes place overseas.<sup>85</sup> This is referred to as the extraterritorial application of law.<sup>86</sup> Although the United States has always been cautious about holding its citizens criminally liable for conduct that both occurs outside of the country and is in accord with the laws of the country where the events take place, in fact there are many existing statutory schemes that do just that.<sup>87</sup> The United States, Canada, and the United Kingdom have an array of anti-fraud, anti-corruption, and anti-bribery laws that apply to U.S. companies operating overseas.<sup>88</sup>

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84. See Duguet et al., *supra* note 72, at 988, 990 (specifying that in addition to the worldwide guidelines and recommendations, specific countries have adopted laws or regulations for human subjects research).

85. See Austen L. Parrish, *The Effects Test: Extraterritoriality's Fifth Business*, 61 VAND. L. REV. 1455, 1456 (2008) (explaining that the world has recently seen a tremendous expansion in countries using extraterritorial laws).

86. See RESTATEMENT (THIRD) OF FOREIGN RELATIONS LAW OF THE U.S. § 402.1(c) (1987) (stating that a state has jurisdiction to prescribe law with respect to conduct outside its territory that has or is intended to have substantial effect within its territory); Parrish, *supra* note 85, at 1496, (explaining that the jurisdiction to prescribe discussed in the Restatement § 402 is also known as extraterritoriality).

87. See Dodge, *supra* note 78, at 86 (citing RESTATEMENT, *supra* note 86, § 415 Reporter's n.2 (commenting on Justice Holmes' conclusion in *Am. Banana Co. v. United Fruit Co.*, 213 U.S. 347, 356 (1909) "that the character of an act as lawful or unlawful must be determined wholly by the law of the country where the act is done" but observing that "[t]his statement, though still often quoted, does not reflect the current law of the United States")); see also *supra* notes 79–81 (providing examples of U.S. laws with extraterritorial implications).

88. See generally Gordon Kaiser, *Corruption in the Energy Sector: Criminal Fines, Civil Judgments, and Lost Arbitrations*, 34 ENERGY L.J. 193, 195, 199 (2013) (describing anti-bribery, anti-fraud and anti-corruption laws in the energy sector).

A common focus of these laws is an effort to prevent human trafficking.<sup>89</sup> Another is to enhance the enforcement of human rights laws.<sup>90</sup> The primary way a country can impose its own laws on activities that occur outside of its territorial jurisdiction is to hold accountable individuals within its jurisdiction for acts done outside of it.

So, for example, a pharmaceutical company that goes to Country A and engages in activity that would be illegal in Country B can find itself a defendant in a lawsuit or even criminally indicted according to the laws of Country B. Country B can seize whatever assets the defendant has in Country B and subject the defendant to the penalties of default, should the defendant or its officers return.<sup>91</sup>

Not all countries are helpless in the face of violations of their laws regarding human subject research protection. India has taken a direct approach to what it considers to be exploitation of its population by drug researchers coming from overseas.<sup>92</sup> Faced with the problem of an inability to oversee individual clinical trials involving its citizens, India took the dramatic step of banning all human subject research by foreign companies involving Indian citizens.<sup>93</sup> This has provoked considerable

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89. See Trafficking Victims Protection Act (TVPA), 22 U.S.C. §§ 7101–7112 (2012) (regulating trafficking in persons that may occur or originate in a foreign jurisdiction); see also 8 C.F.R. § 214.11 (2014) (granting special immigration status to alien victims of trafficking); Vicki Trapalis, *Extraterritorial Jurisdiction: A Step Towards Eradicating the Trafficking of Women Into Greece for Forced Prostitution*, 32 GOLDEN GATE U. L. REV. 207, 227 (2002) (observing that the Convention Against Transnational Organized Crime should not be viewed as a limitation to extraterritorial jurisdiction).

90. Danielle Ireland-Piper, *Prosecutions of Extraterritorial Criminal Conduct and the Abuse of Rights Doctrine*, 9 UTRECHT L. REV. 68, 70, 79 (2013), available at <https://www.utrechtlawreview.org/index.php/ulr/article/view/243/237>.

91. For example, in order to sell diamonds in the United States and for its executives to enter the country without fear of arrest, De Beers had to negotiate a guilty plea to violation of U.S. price-fixing laws. Stephen Labaton, *De Beers Agrees to Guilty Plea to Re-Enter the U.S. Market*, N.Y. TIMES, July 10, 2004, at C1.

92. Laasya Sahmita, *Badly Run Trials Behind Indian Drug Testing Freeze*, NEW SCIENTIST (Oct. 17, 2013, 3:30 PM), <http://www.newscientist.com/article/dn24421-badly-run-trials-behind-indian-drug-testing-freeze.html> (noting that the Indian Supreme Court issued an opinion halting 162 clinical trials).

93. *Id.*

protest within the country because of its negative effect on the economy.<sup>94</sup> As one pharmaceutical executive explained:

winning back the confidence of the CROs [clinical research organizations] will be a challenging and uphill task. Given some of the sensationalism and misinformed reporting of clinical research in India, there is a need to garner the trust of investigators in conducting clinical research in the country and of the general public in participating in clinical research. It will take several months before we see clinical research back in India on track.<sup>95</sup>

### C. *Law of the Country Where the Product Will Be Sold*

The third option for legal regulation, concerning research that results in marketable product, is the law of whichever country where the product is to be sold.<sup>96</sup> As of 2014, most of the countries in which pharmaceutical companies test new products have internal laws protecting human subjects.<sup>97</sup> Many, like South Africa and India, have infrastructures quite similar to those in the United States, Europe, and the EU.<sup>98</sup> However, given the amount of money companies have to spend on

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94. See Nandita Vijay, *ISCR Notes Positive Response Of Regulatory Authorities, Hopeful of Return of Business For Trials*, PHARMABIZ.COM (Aug. 5, 2014), <http://www.pharmabiz.com/NewsDetails.aspx?aid=83318&sid=1> (stating that many Indian clinical testing companies have moved their business overseas); see also Kiran Mazumdar *Asks PM to Heal Pharma Sector*, BUS. STANDARD (July 30, 2014), [http://www.business-standard.com/article/companies/kiran-mazumdar-asks-pm-to-heal-pharma-sector-114073001186\\_1.html](http://www.business-standard.com/article/companies/kiran-mazumdar-asks-pm-to-heal-pharma-sector-114073001186_1.html) (noting that Indian industry leaders say that the current regulatory environment has harmed the Indian pharmaceutical economy); see also Soumonty Kanungo, *This Is Going to Be Challenging Year in the US Market: Glenn Saldanha*, DNA INDIA (July 28, 2014), <http://www.dnaindia.com/money/report-this-is-going-to-be-challenging-year-in-the-us-market-glenn-saldanha-2005816> (providing comments from the chairman and managing director of Glenmark Pharmaceuticals regarding regulatory hurdles in the Indian clinical testing market).

95. Vijay, *supra* note 94.

96. See Duguet et al., *supra* note 72, at 988, 990, 992 (explaining that adherence to FDA regulations is required to sell a drug in the U.S. market).

97. See OFFICE FOR HUMAN RESEARCH PROTS., *supra* note 73 (showing 107 countries having over 1,000 laws, regulations, or guidelines protecting human subjects).

98. See, e.g., HUMAN RIGHTS WATCH, *WORLD REPORT 2013*, at 159, 639 (2013) (noting that the United States has constitutional protections for human rights and that South Africa has “strong constitutional protections for human rights”).

conducting these studies, the reality is that having laws is not the same as enforcing them. For example, a recent posting by the Cato Institute for the benefit of those seeking to conduct human subject research in South Africa assures that

[w]hilst the regulatory process in South Africa may seem lengthy, the good news is that in most instances contract negotiations are relatively simple. Doctors in private institutions are self-employed and negotiate the contracts themselves, the largest amount of haggling occurs over the budget. Public sector sites may require additional documentation but even these negotiations can be finalized before [regulatory authority] approval is received. This means that once the [regulatory authority] approval is in place, sites can usually be initiated shortly thereafter.<sup>99</sup>

Each country maintains sovereignty over the products that can be sold within its borders, but not all exercise that sovereignty. Even when they do, few countries require that applicants certify that the research supporting their application was conducted under the legal standards they would apply to research taking place in their own country.<sup>100</sup> Professor Fazak Khan has suggested a means of combating this practice known as “market exclusion.”<sup>101</sup>

#### *D. International Law*

##### *1. The International Conference on Harmonization (ICH)*

The International Conference on Harmonization (ICH) is a nongovernmental, independent organization that has contracted with the United States to establish what it describes as

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99. Nicola Main et al., *Clinical Trials in South Africa 101*, ASK CATO (Apr. 7, 2011), <http://www.ask-cato.com/2011/04/clinical-trials-in-south-africa-101>.

100. See Jennifer S. Bard, *Closing the Gaps in Human Subject Research Law: Regulating Clinical Research Conducted Outside of the United States*, 21 ANNALS HEALTH L. 201, 205 (2012) (“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.”).

101. Fazal Khan, *Promoting Ethical Standards in Globalized Drug Trials Through Market Exclusion*, DEAN RUSK CTR. NEWSLETTER (Dean Rusk Ctr., Athens, Ga.) Winter/Spring 2008, at 11.

Guidelines for Good Clinical Practice (GCP).<sup>102</sup> The motivation for developing the GCP was the need for consistent “across-the-board extrapolation of data” from studies that involved “subjects from many populations in many parts of the world.”<sup>103</sup> These are offered as international norms for human subject protection in clinical trials.<sup>104</sup> The ICH has no enforcement power of its own, but, like other sources of model rules or laws, it relies on its guidelines being adopted into law by countries that either conduct international human subject research or regulate the sale of these products to its citizens.<sup>105</sup> The United States is among the many countries that have adopted GCP as requirements for all clinical trials, whether conducted in the United States or abroad.<sup>106</sup> Those satisfied with the current state of legal protection for human subjects of research point to the existence of international standards, like the Helsinki Accord.<sup>107</sup>

Although one of the areas of harmonization is human subject safety, the primary goal was to make it easier to

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102. See J. John Lee, *What is Past is Prologue: The International Conference on Harmonization and Lessons Learned From European Drug Regulations Harmonization*, 26 U. PA. J. INT’L ECON. L. 151, 179–80 (2005) (recounting the process of developing the ICH guidelines); Charles W. Schmidt, *Monitoring Research Overseas: Clinical Trial Conduct Reaches Global Harmonization*, 4 MODERN DRUG DISCOVERY 2 (2001), available at <http://pubs.acs.org/subscribe/journals/mdd/v04/i02/html/rules.html> (noting that ICH released the GCP in 1996).

103. J. A. Molzon et al., *The Value and Benefits of the International Conference on Harmonisation to Drug Regulatory Authorities: Advancing Harmonization for Better Public Health*, 89 CLINICAL PHARMACOLOGY & THERAPEUTICS 503, 508 (2011).

104. See Schmidt, *supra* note 102 (discussing how the GCP “standards are accepted as official guidance for conducting clinical trials in the United States as well as relevant agencies in the European Union countries and Japan”).

105. See Dan Kidd, *The International Conference on Harmonization of Pharmaceutical Regulations, the European Medicines Evaluation Agency, and the FDA: Who’s Zooming Who?*, 4 IND. J. GLOBAL LEGAL STUD. 183 (1996) (discussing how ICH guidelines are subject to the will of each country to enforce and are not binding unless adopted into law).

106. See 21 C.F.R. § 312.120 (2013) (stating that foreign studies must comply with GCP standards to be accepted by the FDA).

107. Andreas Möckli, *Drug Companies Accused of Exploiting the Poor in Human Clinical Trials*, WORLD CRUNCH (June 21, 2011), <http://www.worldcrunch.com/drug-companies-accused-exploiting-poor-human-clinical-trials/culture-society/drug-companies-accused-of-exploiting-the-poor-in-human-clinical-trials/c3s3332/>.

communicate with regulators of the ICH to develop consistent standards of quality.<sup>108</sup> Not all countries agree that the ICH guidelines provide sufficient levels of human subject research protection. For example, India has “block[ed]” the WHO’s efforts to adopt ICH standards.<sup>109</sup>

## 2. Criticisms of ICH Standards

Many ethicists assert that the GCP standards are ethically less stringent than the provisions of the Declaration of Helsinki. Researchers from South Africa’s Stellenbosch University put it plainly:

The 2008 revision of the DoH is more ethically demanding than the ICH-GCP, and addresses moral issues that the ICH-GCP guidelines do not. These include the restriction of placebo controls in clinical trials in developing countries; the disclosure of the trial design to the public; a requirement that the population in which the research is conducted should benefit from it, particularly in developing countries, and that participants should have post-trial access to treatment; the need to publish results; and the disclosure of conflicts of interest.<sup>110</sup>

A study conducted by a team of bioethicists studied “nearly 6,000 consolidated standards” adopted internationally, including the World Medical Association’s Declaration of Helsinki, guidelines by the Council for International Organizations of Medical Sciences, the ICH’s GCP, and the Consolidated Standards of Reporting Trials Group’s reporting norms, in addition to the influential U.S. Federal Common Rule, FDA

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108. Molzon et al., *supra* note 103, at 508 (“Originally, the ICH focused on input by industry—the technical submission requirements for pharmaceuticals for human use. Harmonizing the differences in these requirements through ICH guidelines...helped industry reduce development time and save resources.”).

109. Rema Nagarajan, *India Thwarts Big Pharma Push at WHO Assembly*, TIMES OF INDIA (June 15, 2014), <http://timesofindia.indiatimes.com/india/India-thwarts-Big-Pharma-push-at-WHO-assembly/articleshow/36573586.cms>.

110. L. J. Burgess & D. Pretorius, *FDA Abandons the Declaration of Helsinki: The Effect on the Ethics of Clinical Trial Conduct in South Africa and Other Developing Countries*, S. AFR. J. BIOETHICS & L., Dec. 2012, at 87, 87 (citations omitted), available at <http://www.ajol.info/index.php/sajbl/article/download/83499/73534>.

regulations, and information sheets by the U.S. Department of Health and Human Services (HHS), as well as “norms published at more local levels by official agencies and professional groups.”<sup>111</sup> The researchers found “15 substantive topics of conflict” among the standards.<sup>112</sup> Although not all were major, their findings demonstrate the difficulty of “harmonization” across ethical standards of human subject research protection.<sup>113</sup>

## VI. CURRENT REGULATORY SCHEME IN THE UNITED STATES

### A. General Overview

Although many histories of human subject research regulation in the United States create a narrative of the world’s horror at the crimes perpetrated by physicians and scientists in Nazi Germany against those imprisoned in concentration camps, in fact the first effective laws were not passed until the mid-1970’s, thirty years after the war ended.<sup>114</sup> It took a completely homegrown violation of basic human dignity in the form of experiments conducted by the United States Public Health Service against indigent, African-American sharecroppers in Alabama to make the public and the legislatures who represented them, aware of the need for oversight.<sup>115</sup> The resulting legislation, usually described as 45 C.F.R. 46, developed an ethics oversight structure that all recipients of, at first, federal funding from

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111. Jacob M. Kolman et al., *Conflicts Among Multinational Ethical and Scientific Standards for Clinical Trials of Therapeutic Interventions*, 40 J.L. MED. & ETHICS 99, 99, 109 (2012).

112. *Id.* at 102.

113. See INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, COUNCIL FOR INT’L ORGS. OF MED. SCIS. & WORLD HEALTH ORG. 7–9 (2002), available at [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf) (discussing the difficulty in reconciling conflicting ethical views when developing guidelines).

114. Bard, *supra* note 3, at 13; see also *Protecting Human Research Participants*, NIH OFF. OF EXTRAMURAL RES., [https://phrp.nihtraining.com/history/07\\_history.php](https://phrp.nihtraining.com/history/07_history.php) (last visited Sept. 5, 2014) (providing a graphic representation of the history of human subjects of research protection in the United States).

115. See Bard, *supra* note 3, at 14 (discussing the Tuskegee Study); see also *The Tuskegee Timeline*, CTRS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/tuskegee/timeline.htm> (last visited Sept. 5, 2014) (providing an overview of the Tuskegee Study).

HHS, had to follow.<sup>116</sup> Within a few years, all the agencies in the federal government agreed to adopt these rules, now called the “Common Rule” for research they funded. Over time, the FDA, a branch of HHS, has agreed to apply most of the Common Rule to clinical drug trials taking place in the United States. But from the beginning, there were considerable gaps. These provisions, however, never extended beyond research conducted by, funded by, or overseen by the federal government.

*B. Regulation of Human Subject Research Supporting an Application to Sell a Drug, Device, or Biologic in the United States*

The first legal protections of human subjects funded by the U.S. Government were passed in 1974.<sup>117</sup> They took on their current structure through the publication and revision of HHS and FDA regulations in the early 1980’s.<sup>118</sup> Before any drug, device, or biologic can be marketed in the United States, it must be reviewed by the FDA’s Center for Drug Evaluation and Research (CDER), whose mission “is to ensure that drugs marketed in this country are safe and effective.”<sup>119</sup> The CDER requires that companies providing data supporting an application for approval to market a drug prove that the testing was conducted in “adherence to principles of good clinical practices (GCPs).”<sup>120</sup> This is an umbrella term encompassing the integrity of manufacturing of the drug being tested, the methods used to test the drug and record data, and the provision of “adequate

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116. Bard, *supra* note 3, at 15; *Human Subjects Research (45 CFR 46)*, U.S. DEP’T OF HEALTH & HUMAN SERVS., <http://www.hhs.gov/ohrp/humansubjects/guidance> (last visited Sept. 5, 2014).

117. *Regulations*, U.S. DEP’T OF HEALTH & HUMAN SERVS., <http://www.hhs.gov/ohrp/humansubjects> (last updated Apr. 29, 2014).

118. See *Protecting Human Research Participants*, *supra* note 114 (providing a graphic representation of the history of human subjects of research protection in the United States).

119. *How Drugs are Developed and Approved*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm> (last updated Feb. 13, 2014).

120. See 21 C.F.R. § 312.120 (2013) (declaring that foreign studies must comply with GCP standards to be accepted by the FDA).

human subject protection (HSP).”<sup>121</sup> From the FDA’s perspective, “[a]dherence to the principles of good clinical practices (GCPs), including adequate human subject protection (HSP) is universally recognized as a critical requirement to the conduct of research involving human subjects.”<sup>122</sup>

### 1. *The IND Process in the United States*

The first step for companies seeking to test a new drug, biological, or device within the United States by giving it to humans is to contact the FDA for an Investigational New Drug (IND) Application, which allows them to go ahead with a clinical drug trial.<sup>123</sup> The company must provide the FDA with the data it gathered in the laboratory and animal testing results that support its claim that the drug is safe enough to give to humans, even though its full safety profile is not yet known.<sup>124</sup> According to recent guidance from the FDA to drug sponsors, the FDA’s primary concern “[w]hen reviewing an original IND submission or planning for a pre-IND meeting . . . is the safety of the

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121. See Lester “Jao” Lacorte, MD, Medical Officer, Ctr. for Devices and Radiological Health, *Good Clinical Practice 101: An Introduction* 3, 6, available at <http://www.fda.gov/downloads/Training/CDRHLearn/UCM176414.pdf> (defining GCP and the goals thereof); see also CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., *GUIDANCE FOR INDUSTRY E6 GOOD CLINICAL PRACTICE: CONSOLIDATED GUIDANCE* ¶ 1.24 (1996), available at <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf> (defining GCP as “a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.”).

122. *Clinical Trials and Human Subject Protection*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm> (last updated July 15, 2014).

123. See *The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last updated May 28, 2014).

124. See *How FDA Evaluates Regulated Products: Drugs*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm269834.htm> (last updated Sept. 16, 2014) (“The first step for a company seeking approval to sell a new drug is to perform laboratory and animal tests to learn how the drug works and if it will be safe enough to be tested in humans.”).

subjects who will receive the drug during the proposed clinical trial.”<sup>125</sup>

However, clinical trials that take place outside the United States do not require an IND, and therefore can completely avoid any kind of preliminary FDA review, including any review of how human subjects will be kept safe. The only contact a sponsor has with the FDA is after the clinical trials are complete and it wants to use the data to support approval to market the drug in the United States. The FDA has the legal authority to require sponsors to certify that the data they are using was obtained under the same human subject protections as would be applicable in the United States. However, the FDA has made clear that this is not necessary.<sup>126</sup>

At this last stage, after all the human trials are complete, the FDA could, but does not, require that all companies certify that the humans involved in the testing were given the same protections as they would be had they been located in the United States. So even though the company would not have had to get pre-approval to start testing their product on humans, once they wanted to use that data to support their application to the FDA they would have to show they had done so. This still leaves a loophole, because it would only apply to data they wanted to give the FDA in support of their application. If a drug trial overseas did not work out, they were under no obligation to present that information and no one would ever know what happened to the human subjects involved.

With this overview, it is easier to see the difference between the rules that apply to clinical trials that occur in the United States and those that occur outside of it because the FDA’s way of describing these two situations are by contrasting studies that do need pre-approval and those that do not.

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125. OFF. OF NEW DRUGS, U.S. FOOD & DRUG ADMIN., GOOD REVIEW PRACTICE: CLINICAL REVIEW OF INVESTIGATIONAL NEW DRUG APPLICATIONS 2 (2013), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM377108.pdf>.

126. *See* 21 C.F.R. § 314.106 (2013) (allowing the use of foreign data as a sole basis for marketing approval if it meets U.S. criteria for marketing approval); *see also* Bard, *supra* note 3, at 31–32 (discussing the FDA’s lack of oversight of clinical trials that do not fall into the Investigational New Drug category).

The FDA is completely transparent in explaining the difference between the protections required for human subjects inside and outside the United States. It explains that

[t]he final rule replaces the requirement that these studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki (Declaration) issued by the World Medical Association (WMA), specifically the 1989 version (1989 Declaration), with a requirement that the studies be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC). The final rule updates the standards for the acceptance of foreign clinical studies not conducted under an IND and helps ensure the protection of human subjects and the quality and integrity of data obtained from these studies.<sup>127</sup>

*C. Regulation of Human Subject Research Funded by the Federal Government*

The drawback to relying on the FDA, or in a broader sense the HHS, to protect human subjects participating in research is that they depend on Congress for funding, and Congress is very responsive to the interests of the pharmaceutical industry and, to a lesser extent, the academic research establishment. The position of industry is clear. As a pharmaceutical industry executive said in his testimony before the House Energy and Commerce Subcommittee on Health on July 22, 2014, there is worry that “innovation in the U.S. is being eroded by an increasingly costly and cumbersome risk-averse culture in our regulatory and payment systems.”<sup>128</sup>

The pharmaceutical industry is also very effective in mobilizing patient advocates who complain that regulatory barriers delay the discovery and availability of treatments and cures for serious illnesses.<sup>129</sup> Congress is now, and historically

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127. Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 73 Fed. Reg. 22800 (Apr. 28, 2008) (to be codified in 21 C.F.R. § 312.120).

128. *21st Century Cures: Examining Barriers to Ongoing Evidence Development and Communication: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 113th Cong. (2014) (statement of Michael A. Mussallem).

129. *21st Century Cures: Modernizing Clinical Trials: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 113th Cong. (2014) (statement of the

has been, sympathetic to their position. Health Subcommittee Chairman Joe Pitts recently criticized the current laws, stating that the “expensive and antiquated clinical trials model is simply not acceptable in the 21st century. We can and must do better because patients deserve better.”<sup>130</sup>

#### *D. Gaps in U.S. Legal Protection*

The federal government does not regulate human subject research unless it is funded by the government and does not require any government agency’s review. Although some states have passed legislation applying the terms of federal law to any research within their borders, most have not.<sup>131</sup> Moreover, no state claims jurisdiction over research that takes place overseas.<sup>132</sup> Therefore, the research conducted by private entities like the Bill & Melinda Gates Foundation and for-profit companies that do not seek to present the data they collect to a government agency are essentially unregulated. As a matter of practice, many non-profit foundations and even private companies do adhere to the FDA’s Good Clinical Practice Standards. But since they do so voluntarily, there is no cause of action available to subjects who suffer harm.

The Gates Foundation’s “Discovery & Translational Sciences program” strives to

create and improve preventive, diagnostic, and therapeutic interventions for infectious diseases as well as other conditions that affect mothers, infants, and children. [It does] this by identifying and filling gaps in scientific knowledge, creating or implementing new technology platforms that can accelerate research in support of [its] goals, and investing in potentially transformative ideas.<sup>133</sup>

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Hon. Joseph R. Pitts, Chairman, Subcomm. on Health).

130. *Id.*; Erica Teichert, *FDA Clinical Trials Need More Flexibility*, *Lawmakers Say*, LAW360 (July 9, 2014), <http://www.law360.com/articles/555714/fda-clinical-trials-need-more-flexibility-lawmakers-say>Teichert.

131. See Bard, *supra* note 3, at 19–20 (noting that some states have already passed laws regulating human subject research occurring within their borders).

132. *Id.*

133. *What We Do: Discovery and Translational Sciences Strategy Overview*, BILL

That is to say that it funds clinical trials just like drug companies but, unlike drug companies, it does not necessarily intend to develop a marketable product that would require FDA approval. Part of what makes them different is that because they are not motivated by profit, they can study new and better uses for existing drugs. But although their motivation may be different, the activity itself, administering drugs to humans in order to get information, is the same.

Interestingly, because the Gates Foundation is not funded by the government and does not seek FDA approval,<sup>134</sup> it is very likely that it would not be bound by federal human subject protections unless it conducted its research through academic medical centers or other institutions that had already agreed with the government to apply the same protections to all subjects.

The Gates Foundation has chosen not to require the institutions and companies it funds to comply with U.S. human subject research protection laws beyond what would be required by the FDA.<sup>135</sup> So if the clinical trial it funds will be conducted overseas and the FDA only requires clinical practice, so does the Gates Foundation.

## *E. U.S. Law*

### *1. The FDA*

The FDA will accept research conducted entirely outside the United States with only a requirement that it meet the “Good Clinical Practice” standard.<sup>136</sup> The FDA has proposed changing

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& MELINDA GATES FOUND., <http://www.gatesfoundation.org/What-We-Do/Global-Health/Discovery-and-Translational-Sciences> (last visited Sept. 5, 2014).

134. See *Who We Are: Financials*, BILL & MELINDA GATES FOUND., <http://www.gatesfoundation.org/Who-We-Are/General-Information/Financials> (last visited Sep. 5, 2014) (explaining funding). See generally Rules & Guidelines Document by Bill & Melinda Gates Found., Simple and Affordable Molecular Testing for Tuberculosis: Request for Letters of Intent (LOI) 10, available at <http://mat1.gting.com/gongyi/2012/1.2ying.docx> (explaining that grant recipients take “full responsibility for all compliance, data safety, monitoring, and audit requirements of the relevant regulatory agencies”).

135. Rules & Guidelines Document, *supra* note 134 (explaining requirements for Gates Foundation funding for clinical trials involving human subjects).

136. CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION

this requirement.<sup>137</sup> These are international norms, not necessarily the same as those imposed on clinical trials taking place in the United States. If a drug trial is conducted entirely outside the United States, it is not necessary to apply in advance to the FDA for IND approval so long as “Good Clinical Practice” guidelines were observed.<sup>138</sup> A company that wants to conduct clinical trials in the United States has the option to do preliminary trials outside the United States and present that data in support of an IND.<sup>139</sup>

## 2. *Alien Tort Claims Act*

The primary method for accessing U.S. courts for a wrong conducted outside of the United States is the Alien Tort Claims Act (ATCA).<sup>140</sup> There are three elements to a suit under the ATCA: “the plaintiff is an alien to the United States; the defendant committed a tort; and the tort was committed in violation of the law of nations or a treaty of the United States. *See* 28 U.S.C. § 1350 (2007).”<sup>141</sup> So far, no individuals have been able to recover under the claim that they were injured overseas during a clinical drug trial conducted by a U.S. company.

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& RESEARCH, U.S. DEPT. OF HEALTH & HUM. SERVS., GUIDANCE FOR INDUSTRY AND FDA STAFF: FDA ACCEPTANCE OF FOREIGN CLINICAL STUDIES NOT CONDUCTED UNDER AN IND: FREQUENTLY ASKED QUESTIONS 1 (2012), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>.

137. *See* Human Subject Protection: Acceptance of Data from Clinical Studies for Medical Devices, 78 Fed. Reg. 12664, 12673 (Feb. 25, 2013); Natalie Blazer, *Regulation of Overseas Clinical Trials: FDA vs. Industry*, WEIL (May 31, 2013), <http://product-liability.weil.com/pharmaceutical-law/regulation-of-overseas-clinical-trials-fda-vs-industry>.

138. Bard, *supra* note 3, at 31–32.

139. *See* Duff Wilson, *6,485 Overseas Clinical Trials and Counting*, N.Y. TIMES (Dec. 2, 2010), <http://prescriptions.blogs.nytimes.com/2010/12/02/6485-overseas-clinical-trials-and-counting> (explaining that clinical trials may be done overseas, but once a company files a New Drug Application, trials must be submitted and may be reviewed).

140. *See generally* Beth Stephens, *The Curious History of The Alien Tort Statute*, 89 NOTRE DAME L. REV. 1467, 1467–68 (2013) (discussing the history of the Alien Tort Statute and noting that it authorizes private foreign parties to bring claims for violations of U.S. law).

141. Michael Traynor & Erin Wallace, *Clinical Trials: Emerging Issues Regarding Globalization of Pharmaceutical Research; Insurance; Informed Consent; Securities Litigation; and Public Policy* (Sept. 6–7, 2007) (unpublished student paper), *available at* [http://www.cooley.com/files/tbl\\_s5SiteRepository/FileUpload21/1348/Article%20-%20Sep%2007%20-%20Traynor%20-%20Clinical%20Trials.pdf](http://www.cooley.com/files/tbl_s5SiteRepository/FileUpload21/1348/Article%20-%20Sep%2007%20-%20Traynor%20-%20Clinical%20Trials.pdf).

## VII. INTERNATIONAL LAW

The World Health Organization (WHO) has standards for human subject research,<sup>142</sup> but they are only binding to the extent a country agrees to follow them.

*A. A Brief History of HSR Regulation*

The first multi-national standard for human subject research came out of collective shock from the atrocities committed by the Nazis against civilians under the guise of medical experimentation. In the trial of these doctors and scientists for war crimes, the Nuremberg Tribunal included in its written opinion ten standards that should, in the future, guide those conducting experiments with humans.<sup>143</sup> Following the promulgation of the Nuremberg Code and the Declaration of Helsinki, individual countries began on their own paths towards regulating human subject research. In the United States, unfortunately, that path resulted in no further regulatory action until 1966, when Dr. Henry Beecher published an article in the *New England Journal of Medicine* reviewing 22 studies conducted in the United States that involved substantial violations of informed consent.<sup>144</sup> The publication of the paper and the ensuing discussion did not, however, result in any changes to the law.<sup>145</sup> It was not until 1972 when the public became aware of activities of the U.S. Public Health Service in the Tuskegee syphilis experiment that Congress became involved.<sup>146</sup>

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142. WORLD HEALTH ORG., STANDARDS AND OPERATIONAL GUIDANCE FOR ETHICS REVIEW OF HEALTH-RELATED RESEARCH WITH HUMAN PARTICIPANTS (2011), available at [http://whqlibdoc.who.int/publications/2011/9789241502948\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241502948_eng.pdf).

143. Evelyne Shuster, *Fifty Years Later: The Significance of the Nuremberg Code*, 337 NEW ENG. J. MED. 1436, 1439 (1997). See *The Nuremberg Code*, U.S. DEPT OF HEALTH & HUM. SERVS., <http://www.hhs.gov/ohrp/archive/nurcode.html> (last updated Nov. 7, 2005), for an enumeration of the ten provisions of the Nuremberg Code.

144. Henry K. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1354-60 (1966).

145. See Bard, *supra* note 3, at 202 (stating that the Medical Research Act, or Common Rule, that protects human subjects was not enacted until 1974).

146. *The Tuskegee Timeline*, *supra* note 115.

By 1974, Congress passed the National Research Act, which authorized the creation of yet another committee, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, to “identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects.”<sup>147</sup> The committee published its findings in a document now referred to as the Belmont Report, and Congress translated the recommendations into regulations shortly thereafter.<sup>148</sup> They are often called collectively “the Common Rule” because they have been adopted by most federal agencies that fund human subject research.<sup>149</sup>

*B. Laws of Individual Country Where Research Is Conducted*

There are few countries where large amounts of human subject research is conducted that lack legal protections.<sup>150</sup> However, it is one thing to have regulations and another to enforce them. Also, even if enforced, the interpretation of a provision such as “all subjects must give informed consent” can vary considerably. For example, the Indian Council of Medical Research’s guidelines<sup>151</sup> are quite similar to those found in the United States.

South Africa has included human subject research protection in its constitution.<sup>152</sup> The regulations implementing this principle are strongly worded and reflect international norms. It has also

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147. NAT’L COMM’N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979), *available at* <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.

148. *See* Bard, *supra* note 3, at 202 (explaining that the United States enacted the Medical Research Act of 1974, which is now often referred to as “the Common Rule”); *see also* 45 C.F.R. §§ 46.101–46.505 (2009) (outlining the basic HHS policy for protection of human research subjects).

149. Bard, *supra* note 3, at 202.

150. *See supra* note 97 and accompanying text.

151. *Guidelines for Preparing Standard Operating Procedures (SOP) for Institutional Ethics Committee for Human Research*, INDIAN COUNCIL OF MED. RESEARCH, [http://icmr.nic.in/ethics\\_SOP.pdf](http://icmr.nic.in/ethics_SOP.pdf) (last visited Oct. 3, 2014).

152. S. AFR. CONST., 1996. Section 12(2)(c) states, “Everyone has the right to bodily and psychological integrity, which includes the right . . . not to be subjected to medical or scientific experiments without their informed consent.” *Id.* § 12(2)(c).

enacted relevant regulations.<sup>153</sup>

### *C. Pitfalls and Risks*

Every sovereign nation has the right to set its own criteria for human subject research protection. But equally, all nations have the ability and right to decide what products they will let into their country and how they will regulate the behavior of their citizens when they go overseas. The United States has already established ethical guidelines on the manufacturing of clothing and the importation of endangered species. It has also extended U.S. criminal jurisdiction for child sex-trafficking by U.S. citizens in other countries.<sup>154</sup> So its decision not to require that drug manufacturers afford the same protection to human subjects outside the United States as those within it is an expression of preference, not a lack of ability to regulate.

Although the United States is not the only purchaser of products developed overseas, it has such a substantial market-share, that its decision to extend protection would likely affect manufacturers' behavior. However, applying U.S.-style protections comes with risks. It is difficult to evaluate the extent to which the pharmaceutical industry's reflexive response to any regulation will prevent them from developing and making available lifesaving drugs or will somehow require them to stop manufacturing existing ones. With few exceptions, the United States has ceded the development and manufacture of drugs to private companies, which must answer to their shareholders, not to the needs of their country.

This article offers tools to help improve decisions about when all researchers, not just pharmaceutical companies, must offer more protection in order to gain access to the U.S. market. It suggests distinguishing between the level of acceptable risk when research is conducted overseas by necessity, as opposed to convenience or to circumvent U.S. law, or to exploit the vulnerability of populations with limited financial resources and without access to medical care.

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153. Medicines and Related Substances Control Act No. 101 of 1965 (S. Afr.); South African Medical Research Council Act of 1991 (S. Afr.).

154. 18 U.S.C. § 1591 (2013).

This is a difficult problem, but developing a way of describing the different scenarios will be a strong first step in developing effective legislative or market-based strategies to protect people who risk their own health in order to test drugs that they are unlikely to benefit from themselves.

### VIII. CONCLUSION

This article presents two things: first, a taxonomy for describing human subject research studies that are conducted outside of the researchers' home country, and, second, an overview of the kind of legal systems applicable in each scenario. In so doing, it points out the considerable gaps in regulation that result in much human subject research being conducted without the protection and oversight that would be required in the researchers' home country. Finally, this article highlights the 2008 rule adopted by the U.S. Food and Drug Administration to accept data from clinical trials conducted overseas in which the human subjects were not afforded the same protection as they would in the United States. In concluding, it notes that although developing countries can protect their citizens by either banning clinical trials conducted by foreign countries, as India has, or by passing a version of the "boomerang" statutes used by South American countries to protect against environmental damage by U.S. companies, this is a high burden. The most effective way to assure that those who test the drugs we take in the United States are offered full protection is to require sponsors to follow the same rules overseas as they would in the United States. Otherwise, we in the United States are imposing risks on others that we would not be willing to take ourselves.