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For the Love of Drugs: Using Pharmaceutical Clinical Trials Abroad to Profit Off the Poor

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INTRODUCTION

"No, there are no murders in Africa. Only regrettable deaths. And from those deaths we derive the benefits of civilization, benefits we can afford so easily . . . because those lives were bought so cheaply."[1]

The global pharmaceutical market is worth $300 billion a year, a figure that is expected to increase to $400 billion within the next three years.[2] In 2012 alone, the 11 largest global pharmaceutical companies raked in nearly $85 billion in net profits,[3] and drug companies' CEOs drew virtually $200 million in total compensation.[4] Profits, however, require sacrifices. While

* Breanne Schuster is a recent graduate of Seattle University School of Law and a former Executive Editor of the *Seattle Journal for Social Justice*. She would like to thank the journal for choosing her article for publication as well as the editors who dedicated their time and expertise to this piece. Breanne would also like to thank all of the amazing people in her life who have continually kept her sane, motivated, and smiling.

[1] THE CONSTANT GARDENER (Focus Features 2005) (based off the novel of the same title by John le Carre). It is alleged that le Carre drew his inspiration for the book from the Trovan pharmaceutical scandal. *See generally* Jim Edwards, *Claim: LeCarre's "The Constant Gardener" Was Based on Pfizer Trovan Case*, CBS MONEYWATCH (Feb. 17, 2009, 9:39 PM), http://www.cbsnews.com/8301-505123_162-42840653/claim-lecarres-the-constant-gardener-was-based-on-pfizer-trovan-case/.

[2] *Pharmaceutical Industry*, *Trade, Foreign Policy, Diplomacy and Health,* WORLD HEALTH ORG., http://www.who.int/trade/glossary/story073/en/ (last visited Feb. 18, 2015) [hereinafter WHO].

[3] Thom Hartmann, *11 Major Drug Companies Raked in $85 Billion Last Year, and Left Many to Die Who Couldn't Buy Their Pricey Drugs*, ALTERNET (Apr. 30, 2013), http://www.alternet.org/11-major-drug-companies-raked-85-.billion-last-year-and-left-many-die-who-couldnt-buy-their-pricey.

[4] Ethan Rome, *Big Pharma CEOs Rake in $1.57 Billion in Pay,* HUFFINGTON POST (May 8, 2013 8:19 AM), http://www.huffingtonpost.com/ethan-rome/big-pharma-ceo-pay_b_3236641.html.

pharmaceutical companies have seen a near 50 percent increase in profits since 2005,[5] India has watched almost 3,000 of its citizens lose their lives to support these industry gains.[6] India is just one of the emerging hot spots for clinical trials; much of the developing world is vulnerable to pharmaceutical invasion.[7] The more unfamiliar and remote the city might appear to the average layperson, the more attractive it seems to be to a company or institution. Desperate populations are prime candidates for clinical trials, and it is clear that the sponsors[8] of these trials are able to get away with virtually anything. In India, only 82 people out of 2,868 have been compensated thus far for deaths occurring during recent clinical trials.[9]

Since 1990, drug trials conducted in foreign countries have increased over 2,000 percent.[10] In 2010, Inspector General of the Department of Health and Human Services Daniel Levinson issued a report titled *Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials*, which found that at least 80 percent of drugs approved for sale in the United States were based off trials conducted either primarily or entirely in

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[5] Diane Archer, *Strengthen Medicare: End Drug Company Price Setting*, HEALTH AFFAIRS BLOG (May 28, 2013), http://healthaffairs.org/blog/2013/05/28/strengthen-medicare-end-drug-company-price-setting/.

[6] Ranjita Biswas, *Over 2,500 Deaths During Indian Clinical Trials*, INTER PRESS SERV. NEWS AGENCY (Nov. 5 2013), http://www.ipsnews.net/2013/11/over-2500-deaths-during-indian-clinical-trials/.

[7] *See*, *e.g.*, Michael Carome, *Unethical Clinical Trials Still Being Conducted in Developing Countries*, HUFFINGTON POST (Dec. 3, 2014), http://www.huffingtonpost.com/michael-carome-md/unethical-clinical-trials_b_5927660.html.

[8] 21 C.F.R. § 50.3(d)–(e) (2000) (defining a sponsor as the person who initiates a clinical trial, as opposed to an investigator, who actually conducts the clinical trial).

[9] S. Srinivasan, *When Clinical Trials Become Dangerous*, THE HINDU BUS. LINE (Oct. 15, 2013), http://www.thehindubusinessline.com/opinion/when-clinical-trials-become-dangerous/article5237461.ece.

[10] Donald L. Barlett & James B. Steele, *Deadly Medicine,* VANITY FAIR (Jan. 2011), *available at* http://www.vanityfair.com/politics/features/2011/01/deadly-medicine-201101.

a foreign country.[11] While Federal Drug Administration (FDA)-regulated trials abroad have consistently increased every year in the past decade, clinical trials in the United States have seen a 5.5 percent annual decline.[12]

This significant increase—and disparity—is troublesome because history has demonstrated the frequently unethical nature of clinical trials conducted abroad by US companies and institutions.[13] A number of failed clinical trials have made it clear that the potential profit benefits of these trials receive greater weight than human rights and ethical considerations.

For example, in the early 1990s, there were predictions that Trovafloxacin Mesylate (commonly known as Trovan), an antibiotic sponsored by the pharmaceutical company Pfizer, could be one of the most financially successful new drugs of its kind, with an estimated $1 billion a year in profits.[14] Animal testing suggested that the drug "had life-threatening side effects including joint disease, abnormal cartilage growth, liver damage, and a degenerative bone condition."[15] However, in 1996, a meningitis outbreak in Nigeria presented the perfect opportunity to test these feared effects.[16] Some doctors warned against the experiments, but

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[11] DANIEL R. LEVINSON, DEP'T OF HEALTH AND HUMAN SERV., CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS 10 (June 2010), http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf.

[12] *Id.* at 20.

[13] *E.g.*, Carome, *supra* note 7; SOMO Briefing Paper on Ethics in Clinical Trials, *#1: Examples of Unethical Trials*, SOMO & WEMOS, (Feb. 2008), *available at* http://www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20'Medicijnen'/examples_of_unethical_trials_feb_2008.pdf.

[14] Sonia Shah, *Globalizing Clinical Research,* THE NATION 3 (Jul. 1, 2002), http://www.thenation.com/article/globalizing-clinical-research#; Joe Stephens, *Where Profits and Lives Hang in Balance*, WASH. POST 1 (Dec. 17, 2000), http://www.washingtonpost.com/wp-dyn/content/story/2008/10/01/ST2008100101390.html.

[15] Abdullahi v. Pfizer, Inc., 562 F.3d 163, 169 (2d. Cir. 2009).

[16] Stephens, *supra* note 14.

those who spoke up were dismissed shortly after.[17] An infectious-disease specialist for the company who cautioned executives that the study was "a violation not only of medical ethics but of federal and international laws" was also subsequently fired.[18]

Clinical testing was approved within one day for Kano, Nigeria, and, while Pfizer initially claimed it had secured approval from an ethics committee, evidence suggested that the approval letter was backdated well after the experiments had taken place and that there was no ethics committee in place at the time of "approval."[19] Pfizer eventually conducted its own investigation, which also proved that the certificate was "incorrect."[20]

Prior to the trial, Doctors Without Borders set up a camp nearby to treat patients with known successful (and free) treatment. Subjects[21] in Pfizer's trials of Trovan were not informed of this alternative, nor were they informed of the experimental nature of the study or the risks involved.[22] Participants were not asked for their consent in English or the subjects'

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[17] Tamar Lewin, *Families Sue Pfizer on Test of Antibiotic*, N.Y. TIMES (Aug. 30, 2001), http://www.nytimes.com/2001/08/30/business/families-sue-pfizer-on-test-of-antibiotic.html.

[18] Walter Armstrong, *Did Pfizer Bribe Its Way Out of Criminal Charges in Nigeria?,* THE ATLANTIC (Dec. 27, 2010), http://www.theatlantic.com/international/archive/2010/12/did-pfizer-bribe-its-way-out-of-criminal-charges-in-nigeria/68495/.

[19] *Abdullahi*, 562 F.3d at 170.

[20] Donald McNeil, *Nigerians Receive First Payments for Children who Died in 1996 Meningitis Drug Trial*, N.Y. TIMES (Aug. 11, 2011), http://www.nytimes.com/2011/08/12/world/africa/12nigeria.html?_r=0.

[21] The choice of the word "subjects" is a conscious one. Unlike "participants," who play an active and consensual role in an activity, "subjects" are individuals under the control and authority of a particular body. Furthermore, dissimilar to participants who might expect some sort of benefit for their participation, subjects connotes an ability to use and subsequently abandon the humans, as if they were mice in a science experiment.

[22] Armstrong, *supra* note 18.

native language of Hausa, and no consent forms were filed.[23] Once the trial began, proper protocols per US guidelines continued to be abandoned. For example, blood was not tested upon arrival and subjects showing no improvement were not removed from the trial and given proper treatment, despite the fact that these are common procedures for similar trials conducted in the United States.[24] Additionally, many children received an oral form of the medication even though an IV[25] was the normal and only previously tested protocol, and many were given injections in improper places. Some children in the study received only as much as one-third of the recommended dosage of the control drug ceftriaxone, many allege, in order to boost the apparent success of the trial.[26] There were no specialists or requisite equipment to look for damage to the subjects during and after the studies.[27] And, the sponsor itself admitted that 20 percent of subjects received treatment that deviated from the pre-approved plan of care.[28]

After two weeks, Pfizer left Kano, without leaving records for the majority of its 200 test subjects.[29] The sponsor did, however, leave behind 11 dead children, and many others with brain damage, paralysis, deafness, and slurred speech.[30] After the trials were completed, dozens of discrepancies in test results were discovered.[31]

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[23] David Smith, *Pfizer Pays out to Nigerian Families of Meningitis Drug Trial Victims,* THE GUARDIAN (Aug. 11, 2011), http://www.theguardian.com/world/2011/aug/11/pfizer-nigeria-meningitis-drug-compensation.
[24] Stephens, *supra* note 14, at 5.
[25] An IV (intravenous) is "a device that is used to allow a fluid (such as blood or a liquid medication) to flow directly into a patient's veins[.]" MERRIAM-WEBSTER, http://www.merriam-webster.com/dictionary/iv (last visited Apr. 10, 2015).
[26] Stephens, *supra* note 14, at 5.
[27] *Id.*
[28] *Id.*
[29] *Id.*
[30] Smith, *supra* note 23.
[31] Stephens, *supra* note 14, at 5.

Still, the drug was approved for market in the United States. Even though testing was done solely on children, Trovan was ultimately approved only for people 14 years old and older because of its potential side effects.[32] Europe suspended sales altogether due to its concern about liver toxicity, but the United States found the drug more marketable.[33] That is, until there were so many reports of liver damage and deaths that the FDA had to take the drug off the market. Pfizer raked in millions of dollars before being sued.[34]

Because the company failed to track long-term recovery of its patients, the only reason the scandal was uncovered was because of an investigation completed by the *Washington Post*.[35] Plaintiffs settled with Pfizer out of court, but only after Pfizer allegedly hired investigators to look into evidence of corruption against the Nigerian attorney general in order to dissuade real legal consequences for its actions.[36] The majority of harmed subjects and their families have yet to obtain any actual compensation.[37] The worst part about all of this, however, is that the Trovan scandal is far from unordinary. As Charles Medawar, director of Social Audit, a UK group that monitors the pharmaceutical industry, stated, "This particular case looks to be very bad, but I hardly think it is untypical."[38]

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[32] *Id*.
[33] Smith, *supra* note 23.
[34] *See* Shah, *supra* note 14; Abdullahi v. Pfizer, Inc., 562 F.3d 163, 163 (2d. Cir. 2009).
[35] The *Washington Post* subsequently published a series of articles regarding the Trovan experiments and clinical trials abroad generally. Stephens, *supra* note 14; Mary Pat Flaherty et al., *Testing Tidal Wave Hits Overseas*, WASH. POST, Dec. 18, 2000, at 4, http://www.washingtonpost.com/wp-dyn/content/article/2008/10/01/AR2008100101117.html; Sharon LaFraniere et al., *The Dilemma: Submit or Suffer 'Uninformed Consent' Is Rising Ethic of the Drug Test Boom*, WASH. POST, Dec. 19, 2000, http://www.washingtonpost.com/wp-dyn/content/article/2008/10/01/AR2008100101150.html?sid=ST2008100101390.
[36] Smith, *supra* note 23.
[37] *Id.*
[38] Jacqui Wise, *Pfizer Accused of Testing New Drug Without Ethical Approval*, BRIT. MED. J. (Jan. 27, 2001), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1119465/.

Despite the significant increase in clinical trials conducted in foreign countries, regulations have remained fairly flexible and consistent with past inadequate standards. Congress and other regulatory agencies, including the FDA, still decline to hold individuals' conduct abroad to the same standards as if they were in the United States. The impact on citizens worldwide has been, and will continue to be, devastating. Thus, US pharmaceutical companies need to be held accountable for trials they conduct abroad.

Part I of this paper will discuss the increase in clinical trials conducted abroad, their potential benefits, and how pharmaceutical companies defend their actions. Part II will discuss why clinical trials conducted in other countries are particularly dangerous and subject to unethical behavior. Part III will discuss how a clinical trial actually works, and the current system of regulation, oversight, and enforcement in place in the United States compared to foreign countries. Part IV will examine the inadequacy of existing regulations and challenges to oversight and enforcement of trials conducted abroad, as well as why potential avenues for relief currently fall short.

Lastly, in Part V, I will offer a number of proposals to ensure pharmaceutical accountability. First, at a minimum, all drug trials conducted abroad should be held to the same requirements as those in the United States. Second, the FDA should require mandatory reporting to a public registry with standardized data, and the FDA should continue to develop more efficient methods of clinical trial risk assessment. Third, more inspections in foreign countries should be conducted, and the FDA should work more closely with foreign bodies to ensure the safety of subjects enrolled in clinical trials overseas. Fourth, the funding of clinical trials should be at the expense of the sponsor conducting the trial. Fifth, populations abroad should be automatically considered "vulnerable" and afforded the same additional protections populations defined as vulnerable in the United States receive. Finally, the FDA should use its authority to

enforce violations of clinical trial standards, and governments worldwide should look to other potential remedies as well to ensure compliance.

I. WHY PHARMACEUTICAL COMPANIES CONDUCT TRIALS ABROAD

Conducting trials abroad has gained popularity for a number of reasons. First, it saves pharmaceutical companies time, money, and resources. Second, while the legitimacy of this argument is debatable, companies articulate that clinical trials conducted in foreign countries benefit global health. As such, pharmaceutical companies have a number of concerns about the increased regulation of these trials.

A. Potential Benefits: Time, Money, and Resource Savings

It should not be much of a surprise that an industry driven by profits outsources; conducting clinical trials outside of the United States is much cheaper and may allow for a speedier generation of profits.[39] A pharmaceutical drug trial costs approximately $180 million in the United States.[40] In other countries, particularly unindustrialized nations, companies often pay less than half as much.[41] One reason for this disparity is that the salaries of physicians, nurses, and study coordinators in other countries are lower.[42] In India, for example, a first-rate academic center charges approximately $1,500 to $2,000 per case report; this is one-tenth of the cost at a second-tier center in the United States.[43] In addition, time can cost

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[39] *See* Tim Sandler, *In India, Oversight Lacking in Outsourced Drug Trials*, NBC NEWS INVESTIGATIONS (Mar. 4, 2012, 5:31 PM), http://investigations.nbcnews.com/_news/2012/03/04/10562883-in-india-oversight-lacking-in-outsourced-drug-trials.
[40] *Id.*
[41] *Id*.
[42] *See generally* Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816 (2009), http://www.nejm.org/doi/full/10.1056/NEJMsb0803929.
[43] *Id.*

millions.[44] In the year 2000, it cost approximately $802 million to produce a new drug. Time accounted for approximately half of that cost.[45] Trials can be completed more quickly outside of the United States. Not only is the time for drug approval generally shorter, but conducting trials abroad may also allow companies to examine seasonal diseases without waiting for the disease to be "in season" in the United States.[46]

It is also easier to find patients, and to find the "right" patients outside of the United States, particularly in developing nations. In the United States, approximately one out of 350 people are willing to do drug testing,[47] and one-third of research and development time is spent on patient recruitment.[48] Relatedly, one report found that the average number of subjects at foreign sites was 505, but domestic sites had a mere 75 subjects.[49] One reason for this phenomenon is that, in many developing countries, patients are without other alternatives to meet their basic needs. 2.6 billion citizens in the world live on less than two dollars a day and they live primarily in developing nations.[50] In some countries, as many as 85 percent of constituents live below the international poverty line.[51] Participating in a clinical trial might be the only method by which a patient

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[44] *Id.*
[45] *Id.* at 817.
[46] Charles W. Schmidt, *Monitoring Research Overseas*, 4 MED. DRUG DISCOVERY 25, 25–26 (2001), *available at* http://pubs.acs.org/subscribe/archive/mdd/v04/i02/html/rules.html. Some diseases, like malaria, are particularly prevalent during certain seasons of the year or in specific climates. By outsourcing trials to countries with different seasons or climates, US companies do not have to wait for the disease to develop at home. *Id.*
[47] Shah, *supra* note 14, at 1.
[48] *See* S. Anoop Pillai et al., *Malady of Clinical Trials in India*, 44 PHARMA TIMES 12, 19 (2012), *available at* https://www.yumpu.com/en/document/view/23478059/malady-of-clinical-trials-in-india-indian-pharmaceutical-association.
[49] LEVINSON, *supra* note 11, at 11.
[50] *See World's Poorest Countries*, INFOPLEASE, http://www.infoplease.com/ipa/A0908763.html (last visited Feb. 19, 2015) (summarizing Human Development Reports).
[51] *See Poverty and Equity Data*, THE WORLD BANK, http://data.worldbank.org/topic/poverty (last visited Feb. 21, 2014).

can pay for food, and, if the patient is ill, it might be the only way they can access any form of medical care. Additionally, doctors are more likely in other countries to mention or recommend trials to patients, either because they may personally receive financial incentives for their encouragement, or they recognize that their patients lack any other options.[52] In many unindustrialized countries, more than half of citizens cannot access "even the most basic drugs."[53] As such, it is also easier to find drug-naïve participants in other countries (which is often ideal for pharmaceutical companies) compared to the United States, where citizens spend an average of $898 on their medication—123 percent more than citizens in developing nations make a year.[54]

Time, money, and resources are also saved because of more lax standards in other countries. Clinical trials in the United States severely strain research budgets and generally strip federal funding.[55] US regulations have recently grown in complexity, increasing the burden on investigators in terms of compliance, documentation, and training.[56] Abroad, there are far fewer regulations and obstacles to bypass when conducting trials. Money is also saved by less competitive markets. The United States, European Economic Community, and Japan account for 90 percent of the world's pharmaceutical research.[57] Thus, when US companies conduct research in

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[52] Dennis M. Coyne, *International Pharmaceutical Mistrials: Existing Law for the Protection of Foreign Human Subjects and a Proposal for Reform*, 29 B.U. INT'L L.J. 427, 429 (2011).

[53] Solomon R. Benatar, *Distributive Justice and Clinical Trials in the Third World*, 22 THEORETICAL MED. BIOETHICS 169, 171 (2001).

[54] *See* Tara Culp-Ressler, *Prescription Drug Spending Drops as Struggling Americans Are Forced to Cut Back on Health Care*, THINKPROGRESS (May 10, 2013, 4:25 PM), http://thinkprogress.org/health/2013/05/10/1993841/prescription-drug-spending-drops/.

[55] Glickman et al., *supra* note 42.

[56] *Id.*

[57] *E.g.*, Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations Among the United States, the European Economic Community, and Japan,* 16 HOUS. J. INT'L L. 665, 667 (1994).

South America, Africa, or most of Asia, they are not competing with many companies from those countries, which saves them additional time, resources, and profits. Further, these trials allow for even greater profits should companies be able to expand in the foreign market. Many governments want testing done on individuals in their own countries before they will allow a drug to be marketed.[58]

History has shown that there are plenty of profits to gain in the field, and the more quickly new drugs are marketed, the faster these profits generate. As the number one monetary contributor to lobbying, pharmaceutical companies have demonstrated that they will do anything to maintain these profits.[59] However, changing patent laws and the increasing cost of research have the potential to offset some of these profits.[60] By looking abroad, pharmaceutical companies are sure to maximize their revenue.

B. Potential Defenses: Pharmaceutical Company Concerns About Additional Regulations

Companies, of course, do not attribute the increase in clinical trials abroad to profit goals, and the sheer increase of clinical trials abroad is not a problem in and of itself. Pharmaceutical companies have presented multiple arguments emphasizing the benefits of these trials. Companies have argued, first, that foreign clinical trials are beneficial for global health. They have claimed that they allow increased access to healthcare and improve the

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[58] Schmidt, *supra* note 46.

[59] *See Top Industries*, OPENSECRETS.ORG CTR. FOR RESPONSIVE POL., http://www.opensecrets.org/lobby/top.php?indexType=i (last visited Mar. 8, 2014).

[60] Blake Wilson, *Clinical Studies Conducted Outside of the United States and Their Role in the Food and Drug Administration's Drug Marketing Approval Process*, 34 U. PA. J. INT'L L. 641, 642 (2013). Patents on pharmaceutical drugs typically last for 20 years, usually with few options to extend, after which the drug may be produced by any "qualified manufacturer" (i.e., it becomes generic). *Id.*

health of children around the world.[61] Drug trials also provide a method for patients who would not otherwise be able to access treatment an opportunity to receive medical care, including medication they may need.[62] Companies additionally claim that foreign physicians, investigators, and medical sites, including hospitals, can get additional experience working with recent drugs and may obtain global recognition for their work.[63] Furthermore, trials abroad may help to shed valuable light on global diseases and ethnic differences that conducting research limited to the United States could not provide.[64] Clinical trials abroad may also foster global clinical innovation and "positive relationships among clinician investigators globally" as well as "answer[] questions about the safety and efficacy of drugs and devices that are of interest throughout the world."[65] There is a great deal of public pressure on pharmaceutical companies and other research institutions to develop life-saving drugs. Conducting research abroad may address these concerns in a quicker and less costly manner.[66]

In light of the alleged benefits of conducting clinical trials abroad, there are also numerous concerns about increasing regulation of these trials conducted overseas. First, pharmaceutical companies have logistical concerns about more stringent standards. They fear that stricter regulations would effectively stop other countries from participating in clinical trials.[67]

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[61] Danielle Burstein et al., *Questions Abound as Pediatric Clinical Trials Move Overseas*, DUKE MED. NEWS AND COMM. (Aug. 23, 2010), http://www.dukehealth.org/health_library/news/questions_abound_as_pediatric_clinical_trials_move_overseas.
[62] Anoop Pillai et al., *supra* note 48.
[63] *Id.*
[64] Ben Hirschler, *Special Report: Big Pharma's Global Guinea Pigs*, REUTERS (May 6, 2011, 11:14 AM), http://www.reuters.com/article/2011/05/06/us-pharmaceuticals-trials-idUSTRE7450SV20110506.
[65] Glickman et al., *supra* note 42.
[66] Burstein et al., *supra* note 61.
[67] Natalie Blazer, *Regulation of Overseas Clinical Trials: FDS vs. Industry*, PROD. LIAB. MONITOR (May 31, 2013), http://product-liability.weil.com/pharmaceutical-law/regulation-of-overseas-clinical-trials-fda-vs-industry/.

Companies also claim that they would be unable to get proper documentation from foreign entities to comply with more rigid rules.[68] Additionally, they argue that the economic incentives (approval of the drug for marketing) are enough on their own to ensure the trials are carried out properly.[69] Lastly, pharmaceutical companies assure activists that additional regulations are unnecessary: that all countries basically have the same standards anyway.[70]

Companies also have some legitimate cultural and ethical claims. Some argue that not allowing these trials is paternalistic. Who are we to tell populations they should not and cannot access experimental treatments?[71] Cultural and ethical imperialism concerns are not limited to those with a stake in the profits.[72] There are fears from multiple organizations that changing regulations to match those of the United States will disrespect the integrity of the community where research is conducted. Additionally, there is concern that some physicians in host countries are opposed to universal requirements. Foreign researchers and physicians might instead prefer that local health experts, bioethicists, and affected groups have the opportunity to assess the risks and benefits of each trial.[73] Relatedly, arguably, changing requirements still does not change the underlying radical power disparity between researchers conducting the clinical trials and the subjects participating in them. There are frequently significant gaps in knowledge, authority, and wealth—is there any way to equalize a relationship where

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[68] *Id*.
[69] Kevin B. O'Reilly, *Outsourcing Clinical Trials: Is It Ethical to Take Drug Studies Abroad?*, AM. MED. NEWS (Sept. 7, 2009), http://www.amednews.com/article/20090907/profession/309079969/4/.
[70] Schmidt, *supra* note 46.
[71] O'Reilly, *supra* note 69.
[72] Makau Wu Mutua, *The Ideology of Human Rights*, 36 VA. J. INT'L L. 589, 592 (1996).
[73] Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT'L L. 513, 544–45 (2002).

one person depends on another for the money to live, or the treatment that could save their life?[74]

II. THE PROBLEM: ETHICAL CONCERNS REGARDING CLINICAL TRIALS CONDUCTED IN FOREIGN COUNTRIES

There are multiple ethical concerns, however, regarding clinical trials conducted abroad. First, research is often conducted on extremely vulnerable populations. Second, trials conducted in foreign countries have the potential for significant fraud because of economic disparities and a lack of oversight and sanctions for abuse. Last, the citizens participating in these trials rarely receive their benefits.

A. Research Is Conducted on Extremely Vulnerable Populations

According to a report by the Centre for Research on Multinational Corporations (SOMO) approximately 40 percent of trials sponsored by the global pharmaceutical industry were conducted in low- and middle-income countries in 2005.[75] This figure is only increasing with the trend of shifting clinical trials overseas to increase profits.[76] Furthermore, in industrialized nations, less than 50 percent of volunteers complete a clinical trial.[77] In developing countries, however, 90 percent of trials or more reach completion.[78] The difference in participation and drug approval between the United States and other nations alone is alarming, and raises serious suspicions about the methods in which the trials were conducted.

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[74] Jacob Schuman, *Beyond Nuremberg: A Critique of "Informed Consent" in Third World Human Subject Research,* 26 J.L. & HEALTH 123, 145 (2012).
[75] Shirley S. Wang et al., *Scrutiny Grows of Trials Abroad*, WALL ST. J. (Dec. 1, 2008, 12:01 AM), http://online.wsj.com/news/articles/SB122809561842168089.
[76] *See id.*
[77] O'Reilly, *supra* note 69.
[78] *Id*.

A number of other factors support these concerns. First of all, as previously demonstrated, trials done abroad are frequently conducted on very vulnerable and desperate populations. Citizens are living in poverty, and often lack alternatives. The little money a sponsor uses to incentivize participation can completely change a participant's life. For example, some sponsors might pay subjects $400 to participate, which in many developing nations is more than a citizen makes in an entire year.[79] As George J. Annas, head of the Health Department at Boston University's School of Public Health, summarized,

> I'd argue you can't do studies ethically in a country where there is no basic health care . . . [.] You can tell a person there that this is research, but they hear they have a chance to get care or else refuse their only good chance at care. How can you put them in that position and then say they are giving informed consent?[80]

Meaningful consent is not only impaired by gross economic disparities, but also by illiteracy and cultural differences.[81] Many countries present high rates of illiteracy (in India, for example, 39 percent of citizens are illiterate) and patients are often uneducated.[82] Many patients are not informed that they are not being treated for a disease, but are instead part of an experiment or research study.[83] For example, seven babies died in Santiago del Estero, Argentina, participating in GlaxoSmithKline's clinical trial for an experimental vaccine.[84] The mothers stated they had no idea their children

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[79] Schuman, *supra* note 74, at 135.
[80] *Id.* at 145–46.
[81] O'Reilly, *supra* note 69; Eliza Barclay, *Sending Medical Research Overseas Troubles Scientists*, NPR, March 4, 2011 12:55 PM, http://www.npr.org/blogs/health/2011/03/04/134176432/sending-medical-research-overseas-troubles-scientists.
[82] O'Reilly, *supra* note 69.
[83] Barlett & Steele, *supra* note 10.
[84] Kelly Hearn, *The Rise of Unregulated Drug Trials in South America*, THE NATION, Oct. 10, 2011, http://www.thenation.com/article/163547/rise-unregulated-drug-trials-south-america?page=0,0.

were enrolled in an experiment.[85] In foreign countries, participants are often not given proper consent forms, or the information needed to understand the ramifications of the trial or their rights as subjects.[86] And if they are, the information is frequently relayed in a language they do not speak.[87] In a survey conducted of South African women who participated in an AIDS experiment, 99 percent stated they did not believe the hospital would allow them to quit once the trial began.[88] While it is imperative to consider the culture of the country research is completed in, evidence demonstrates that, frequently, studies are conducted in ways that are not "optimal for the cultural norms of that neighborhood or environment."[89]

B. There Is Incredible Potential for Abuse and Fraud

While all clinical trials are vulnerable to corruption and fraud, research conducted abroad, particularly in developing nations, is especially at risk for these abuses. First, there is a severe shortage of trained clinical investigators working overseas.[90] Second, there are great incentives for doctors to not only recommend trials to patients, but also lie about trial results. Doctors may get paid multiple times the equivalent of their yearly salary for patient recruitment.[91] For example, Pharmacia and Upjohn, a subsidiary of Pfizer, pays doctors in Latin America approximately $1,300 per patient for an average study.[92] In Budapest, one psychiatrist said US drug companies pay him between $1,000 and $2,000 for his work with each

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[85] *Id.*
[86] LaFraniere et al., *supra* note 35.
[87] *Id*.
[88] *Id.*
[89] Barclay, *supra* note 81 (quoting Robert Califf, vice chancellor for clinical research, Duke Univ.).
[90] Schmidt, *supra* note 46.
[91] Flaherty et al., *supra* note 35, at 4.
[92] *Id.*

clinical trial subject that he can recruit. As he asked, "How can I afford not to?"[93]

Yet, there is no meaningful regulation, oversight, or enforcement to prevent abuse. For example, in 2004, the FDA approved Ketek, a drug developed by Aventis Pharmaceuticals. Just one month prior to approval, one of the company's researchers, Dr. Anne Kirkman-Campbell, was sentenced to 57 months in prison for falsifying at least 91 percent of her data.[94] She had supposedly enrolled over 400 volunteers, including her entire office staff, and approximately 1 percent of the town where she was working.[95] The $400 she collected per patient could not save her from prison.[96] However, results from clinical trials conducted abroad, largely in Hungary, Morocco, Tunisia, and Turkey, gave the FDA the data it needed to approve the drug.[97] Within two years, the FDA received 93 reports of serious adverse reactions to the drug.[98] 12 people died.[99]

If the FDA ignores falsified data in the United States, what happens with data obtained abroad? Francis Weyzig, a researcher at SOMO,[100] indicated that many locals who are carrying out the work abroad face pressure to impress drug company sponsors, who bring them great prestige and money. They may be tempted to "cut corners to boost enrollment or reconcile

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[93] *Id.*
[94] Barlett & Steele, *supra* note 10.
[95] *Id.*
[96] *Id*.
[97] *Id*.
[98] *Id*.
[99] *Id.*
[100] SOMO, http://www.somo.nl/?set_language=en (last visited Feb. 14, 2015). SOMO is the Centre for Research on Multinational Corporations, an "independent, not-for-profit research and network organization working on social, ecological and economic issues related to sustainable development." *Id.*

questionable data[.]"[101] As Dr. Marcia Angell, former editor of the *New England Journal of Medicine*, told *American Prospect*,[102]

> The essence of research is impartiality. . . . There is no substitute for a researcher who is disinterested in the outcome, because it is too easy to bias the results either consciously or unconsciously. What we are seeing now is the disappearance of impartial researchers and institutions . . . . As the economic ties between researchers and industry become virtually ubiquitous and manifold, you have to worry about the quality of the research.[103]

Over 200,000 people in the United States die each year from prescription drugs.[104] That number certainly has the potential to increase exponentially with the growing rate of clinical drug trials abroad.

The potential for abuse and fraud is also significant because there is a lack of sanctions and punishment for those that break the already weak regulations. Countries where experimentation is completed rarely punish violators, and remedies for relief in the United States are scarce. In the 1940s, US researchers infected Guatemalan soldiers, prisoners, prostitutes, and mentally ill people with potentially lethal sexually transmitted diseases (STDs) to test transmission and treatment options.[105] 1,300 people were deliberately exposed to STDs to see if penicillin would prevent infection.[106] Less than half of those infected were treated.[107] At least 83 people died.[108] Despite these sobering statistics, the trials were hidden from the public, only

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[101] Wang et al., *supra* note 75.
[102] *American Prospect* is a bimonthly American political magazine.
[103] Jennifer Washburn, *Undue Influence*, AM. PROSPECT (Dec. 19, 2001), *available at* http://prospect.org/article/undue-influence.
[104] Barlett & Steele, *supra* note 10, at 1.
[105] Ryan Jaslow, *Guatemala Syphilis Experiments in 1940s Called "Chillingly Egregious"*, CBS NEWS (Aug. 21, 2011 11:33 AM), http://www.cbsnews.com/8301-504763_162-20099804-10391704.html.
[106] *Id*.
[107] *Id*.
[108] *Id*.

uncovered when historian Susan M. Reverby of Wellesley College discovered their existence when reading papers from a doctor with the federal government's Public Health Service.[109] The only consequences were a formal apology from President Barack Obama to Guatemala's President Alvaro Colom on the telephone—in other words, nothing.[110]

In Bulgaria, drug researchers conducted experiments without approval.[111] Their punishment consisted of one person receiving a 10-dollar fine from the drug testing police force.[112] Medical Director Janos Borvendeg of Hungary's National Institute of Pharmacy said that if a serious problem were uncovered "we would likely not stop a trial . . . . We would tell them how to improve. I don't like stopping a trial because it costs a company so much to put one on."[113] The director general of the country reiterated that the agency had no provision to fine or bar researchers.[114]

C. There Are Minimal Benefits to Participants Abroad

With all of the risks presented in clinical trials conducted abroad, are they worth it? Who do the trials actually benefit? Very few of the host countries. First, educators, researchers, and other bodies participating in research abroad argue that the supposed goals of clinical innovation and global cooperation are hardly met by clinical trials conducted outside of the United

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[109] Ananya Mandal, *Guatemalan Syphilis Study in 1940's Violated Ethical Standards: US Presidential Commission Report*, NEWS MED. (Aug. 31, 2011 6:09 PM), http://www.news-medical.net/news/20110831/Guatemalan-Syphilis-study-in-1940e28099s-violated-ethical-standards-US-presidential-commission-report.aspx.

[110] Nicholas Johnston, *Obama Apologizes to Guatemala for Syphilis Research*, BLOOMBERG BUSINESS (Oct. 1, 2010 2:51 PM PDT), http://www.bloomberg.com/news/articles/2010-10-01/obama-apologizes-to-guatemala-for-infecting-prisoners-with-stds-in-1940s; Donald G. McNeil Jr., *U.S. Apologizes for Syphilis Tests in Guatemala*, N.Y. TIMES (Oct. 1, 2010), http://www.nytimes.com/2010/10/02/health/research/02infect.html?_r=0.

[111] Flaherty et al., *supra* note 35, at 5.

[112] *Id.*

[113] *Id.*

[114] *Id.*

States.[115] Many have expressed the notion that these trials are simply for numbers, not to foster relationships with other institutions, or to recognize their contributions as scientists and researchers.[116] Professor Mohammed Tikly, Head of Rheumatology at the Chris Hani Baragwanath Teaching Hospital in Soweto, South Africa, stated,

> A disturbing issue for both [private and public] sectors is the fact most trials are designed and finalised before they are brought to us, with little if any room for changing the design or inclusion/exclusion criteria. . . . Really they are using us for our numbers, they are not interested in any intellectual input we make in the developing world; it is only about the number of patients we can recruit. . . . Let's be honest, the drug companies are just trying to sell their products and believe the experts are all in the Northern Hemisphere; we are non-entities.[117]

Second, developing nations account for a very small portion of the market; the United States, European Economic Community, and Japan account for 85 percent of pharmaceutical sales.[118] Most pharmaceutical testing is done for medicines for the developed world in search of cures for ailments like overactive bladders, fibromyalgia,[119] arthritis, obesity, heart disease, and other degenerative diseases.[120] Research is conducted in

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[115] WEMOS FOUND., THE CLINICAL TRIAL INDUSTRY IN SOUTH AFRICA: ETHICS, RULES AND REALITIES 2 (2013), *available at* http://www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20'Medicijnen'/Clinical_Trials_Industry_South_Africa_2013_v3.pdf.
[116] *Id*.
[117] *Id*. at 31 (alteration in original).
[118] Megan Mcardle, *Does the US Really Account for So Much Pharma Profit?*, THE ATLANTIC (Sept. 2, 2009), http://www.theatlantic.com/business/archive/2009/09/does-the-us-really-account-for-so-much-pharma-profit/24465/.
[119] Amanda Gardner, *Many Clinical Trials Moving Overseas: Study Says Trend Raises Ethical, Medical Issues*, US NEWS HEALTH, Feb. 18, 2009, http://health.usnews.com/health-news/managing-your-healthcare/research/articles/2009/02/18/many-clinical-trials-moving-overseas.
[120] Shah, *supra* note 14, at 1.

countries where malaria and tuberculosis run rampant, yet a petty percentage of research funding is devoted to drugs targeting these diseases, the primary ailments of those countries.[121] For example, 0.03 percent of research and development (R&D) between 1975 and 1992 resulted in drugs approved for tropical diseases.[122]

Not only are clinically-tested drugs produced for industrialized nations, but there are also frequently alternatives to the "new and improved" proposed treatments. Most drug research focuses on "follow-ons"—similar treatments to drugs already on the market (i.e., different forms of antibiotics).[123] This makes sense when one considers that pharmaceutical companies are constantly attempting to shave costs. If they can produce the same pill for less money they will fork over the research costs to do so. In fact, pharmaceutical companies only invent approximately half of "innovative" drugs.[124] Pharmaceutical companies consistently claim that pharmaceutical drug prices need to remain high to account for R&D. Yet much of this research is publicly funded, and companies spend significantly more on advertising and marketing than they do on R&D. Currently, companies devote one-third of all sales revenue to advertising and marketing their products; this is approximately double what they spend on R&D.[125] In other words, the majority of pharmaceutical revenue is not spent on curing cancer, but on getting constituents to buy the same pill in a different color.

Third, research is often targeted to ensure that companies continue profit maximization even after drug approval. In 1998, the *Wall Street Journal* found that 25 percent of patients enrolled in clinical trials are enrolled in

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[121] *Id.*
[122] *Id.*
[123] Ed Silverman, *Who Really Discovers Innovative Drugs?*, PHARMALOT (Nov. 16, 2010), http://www.pharmalive.com/who-really-discovers-innovative-drugs.
[124] *Id.*
[125] WHO, *supra* note 2.

post market studies.[126] Theoretically, post market studies are designed to determine the overall risk and benefit balance of the drug in a non-controlled real life setting.[127] Often, however, the trials are "primarily designed to secure a company's market position after a drug has [already] been approved."[128] As a former employee of a major drug company noted, many of these studies are "designed to support and disseminate a marketing message."[129] Instead of efficiency and effectiveness, these studies focus on highlighting potential advantages over competitors, promoting awareness of "invented diseases," increasing product name recognition, and encouraging other marketing strategies.[130]

Even clinical trial testing targeted at tropical diseases or top killers in other countries does not provide patients the assurance they will actually receive any treatment should they participate in the trial because subjects participating in trials abroad are at a greater risk of receiving no treatment than are their US counterparts.[131] The use of placebo-controlled trials is much more popular in other nations, particularly developing and poorer nations like Guatemala, Argentina, Slovakia, Estonia, Czech Republic, Hungary, Latvia, etc.[132] Almost half of the registered studies in those countries use placebo-controlled trials, while between one-fifth and one-third of trials conducted in the United States, United Kingdom, Germany, and France use placebo-controlled trials.[133] In a placebo-controlled trial, some subjects receive a placebo (i.e., no treatment) while others receive the

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[126] Washburn, *supra* note 103.
[127] *Post-Marketing Observational Studies: My Experience in the Drug Industry*, BMJ (June 12, 2012), http://www.bmj.com/content/344/bmj.e3990.
[128] Washburn, *supra* note 103.
[129] BMJ, *supra* note 127.
[130] *Id.*
[131] WEMOS FOUND., *supra* note 115, at 14.
[132] *Id.*
[133] *Id*.

new drug.[134] This is in contrast to studies where some patients receive a satisfactory treatment known to be effective, and some patients receive the new drug.[135] While the merits of the use of placebos in clinical trials is hotly contested, it is worth noting that companies from the United States use them in *significantly* greater percentages in poorer countries.[136] Thus, the most desperate populations may not be able to access treatment, even by participating in dangerous trials.

Subjects may also receive "treatment" that scientists *know* is ineffective at treating the disease. For example, in the early 2000s, a US researcher at the University of Miami conducted tests on children dying of AIDS in the Dominican Republic.[137] The National Institute of Health could afford to treat the children.[138] Instead, however, researchers randomized children into two groups—one group received therapeutic massage and the other (control group) just met with a nurse for "reading, talking, [and] playing quiet games[.]"[139] Researchers paid families $120 and left them without any life-saving drugs.[140] As Marcia Angell, senior lecturer at Harvard Medical School and former editor of *The New England Journal of Medicine*, stated, "This is a terrible study for a number of reasons, including the fact that it is biologically implausible . . . . This would have been impossible to do in the US."[141]

Furthermore, even if a subject is fortunate enough to receive treatment while participating in the trial, he or she seems certain to lose access once

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[134] Sheryl Stolberg, *U.S. AIDS Research Abroad Sets off Outcry over Ethics,* N.Y. TIMES, Sept. 18, 1997, http://www.nytimes.com/1997/09/18/us/us-aids-research-abroad-sets-off-outcry-over-ethics.html.
[135] *Id*.
[136] WEMOS FOUND., *supra* note 115, at 14.
[137] Hearn, *supra* note 84, at 2.
[138] *Id.*
[139] *Id.*
[140] *Id*.
[141] *Id.*

the trial is completed. Even clinical trial testing for the few drugs targeted at diseases or illnesses affecting citizens in developing countries are generally only available to first world nations once the drug is approved.[142] As previously mentioned, host citizens often participate in clinical trials because it is their only method to access the medication they need to survive.[143] Yet, their treatment ends soon after the trial is over.[144] Thus, thousands of participants are left without care while those unwilling to participate in the trial in rich countries reap the benefits.[145] For example, a study in Thailand led to the development of a treatment preventing transmission of HIV from infected mothers to their infants.[146] However, the drug was marketed at a price far beyond what the majority of Thai women could afford, rendering the trial virtually useless to the community where the trial occurred.[147] Numerous trials were conducted in Zambia for nitazoxinade (a drug approved to treat parasite diseases), yet the drug was never even licensed for use in the country.[148]

As FDA Commissioner Margaret Hamburg told Reuter's Health Summit, ensuring proper care for patients is more than just "parachuting in, doing a study and leaving without recognition that these patients have really made a contribution, taken some risks and deserve to be respected and provided with certain broader aspects of care[.]"[149] In answering who these clinical trials benefit, the only truthful answer can be pharmaceutical companies.

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[142] Barlett & Steele, *supra* note 10, at 4.
[143] Schuman, *supra* note 74, at 147.
[144] *Id.*
[145] *Id*.
[146] *See* D.R. Cooley, *Distributive Justice and Clinical Trials in the Third World*, 22 THEORETICAL MED. BIOETHICS 151, 152 (2001).
[147] *Id.*
[148] *Id.*
[149] Hirschler, *supra* note 64.

III. EXISTING RULES AND REGULATIONS: HOW DOES A CLINICAL TRIAL WORK?

The Federal Drug and Cosmetic Act (FDCA), 21 U.S.C. §§ 301–392 (among other requirements) sets out guidelines for the drug approval process.[150] 21 U.S.C. § 355 requires that any person wanting to introduce a new drug within interstate commerce must first file an application with the FDA.[151] The FDCA also requires "all new investigational drugs and biologics to undergo clinical trials on human subjects to demonstrate the safety and efficacy of these products prior to approval for sale in the United States."[152] Data to support these applications may be submitted from the United States (domestic clinical trials) or other countries (foreign clinical trials).[153]

The entity initiating the clinical investigation (but not actually conducting it) is called the sponsor of the clinical trial.[154] Sponsors typically hire clinical investigators, who actually conduct the clinical investigation. Some companies, like Pfizer and Bristol Myers Squibb, have their own research operations in the countries where they conduct clinical trials.[155] Many, however, rely on additional middlemen—contract research organizations (CROs).[156] CROs "recruit patients, conduct tests, and analyze data that will be submitted to the FDA."[157] They also assist with regulatory compliance and marketing and branding.[158] CROs may be foreign, and thus are only

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[150] *See Development and Approval Process (Drugs)*, U.S. FOOD & DRUG ADMIN. (Oct. 27, 2014), http://www.fda.gov/drugs/developmentapprovalprocess/.
[151] *See* 21 U.S.C. § 355 (2013).
[152] LEVINSON, *supra* note 11, at i.
[153] *Id*.
[154] 21. C.F.R. § 50.3 (2013) (defining "sponsor").
[155] Sandler, *supra* note 39.
[156] *See* PHARMALIVE.COM, GLOBAL CONTRACT MANUFACTURING COMPANIES: PHARMACEUTICAL AND BIOTECHNOLOGY 11–13 (2011), *available at* http://www.paragonbioservices.com/LinkClick.aspx?fileticket=CYCb05Z6DIQ%3D&tabid=137.
[157] Sandler, *supra* note 39.
[158] Hearn, *supra* note 84, at 1.

regulated and monitored by the foreign governments. In 2010, the CRO market was worth $20 billion, "an estimated 100 percent jump" from 2000.[159]

A. Trajectory of a Clinical Trial

The Investigational New Drug Application (IND) is where FDA oversight of a clinical trial begins.[160] Sponsors regulated by the FDA who conduct research in the United States must first submit an IND. An IND sets up the procedure for drug testing and must assure a certain level of quality, permit adequate evaluation of the testing, and protect the rights of subjects.[161] The IND must also contain the results of previous preclinical tests and certain information about the drug, including its source and manufacture.[162] Unless the company or institution hears otherwise, it may begin clinical trials 30 days after its application.[163] Once an IND has been submitted, the FDA may inspect a clinical trial at any point during the trial process.[164] INDs, however, are not required for clinical trials that are conducted exclusively outside of the United States.[165] Sponsors may still submit data as a part of their marketing applications for trials conducted without INDs, as well as in support of current INDs.[166]

The first phase of drug testing focuses on clinical pharmacology.[167] It usually involves a small group of typically 15–30 healthy volunteers and, under highly controlled circumstances, is meant to determine "the metaboli[c] and pharmacologic actions of the drug in humans, the side

[159] *Id.*
[160] LEVINSON, *supra* note 11, at 3.
[161] 21 C.F.R. §§ 312, 312.20–312.22, 312.40–312.60 (2015).
[162] *Id.* at § 312.23; LEVINSON, *supra* note 11, at 5.
[163] LEVINSON, *supra* note 11, at 3.
[164] *Id.* at 4.
[165] *Id.* at 3.
[166] 21 C.F.R. §§ 312.210, 314.106, 321.23 (2015).
[167] 21 C.F.R. § 312.21(a) (2015).

effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."[168]

The second phase of clinical trials usually involves several hundred subjects and focuses on the safety and effectiveness of the drug in treating a specific disease.[169] Studies are conducted on individuals with the health problem the drug is intended to target.[170]

The third phase of testing (Phase III) is focused on the widespread clinical use to assess effectiveness and dosage.[171] It seeks to learn more about the benefit risk relationship and involves several hundred to several thousand people.[172] Phase III studies also provide information to disseminate to the general public about the drug, and help determine information to put on drug labeling.[173] This is where the trial is most likely to be outsourced to another country.

Once Phase III trials are completed, the company or institution must file a New Drug Application (NDA) to the FDA's Center for Drug Evaluation and Research (CDER).[174] This entails providing reports of the IND investigations, information about labels, and samples and statements about the drug.[175] This step is the principal regulatory device for controlling drugs in the United States.[176] Once the CDER receives an application, a reviewer first ensures that all necessary application materials have been properly submitted.[177] Afterwards, a series of scientific analyses (i.e., medical,

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[168] *Id.*
[169] Wilson, *supra* note 60, at 648.
[170] *Id.*
[171] *Id.* at 649.
[172] *Id.*
[173] *Id*.
[174] LEVINSON, *supra* note 11, at 5.
[175] *Id.*
[176] *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN. (Feb. 3, 2015), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm.
[177] LEVINSON, *supra* note 11, at 6.

chemistry-based, pharmacology-based, and statistical reviews) are conducted on the pivotal trials (as identified by the sponsor) and other supporting data.[178] Review relies mostly on assurances from sponsors that "Good Clinical Practices" (GCP) were followed, and on supporting procedural descriptions to ensure compliance with the guidelines.[179] If the FDA finds that the clinical trials show the new drug is safe and effective, the trials were done properly, and all of the data is valid, the FDA may approve the drug for marketing in the United States.[180] Alternatively, if the FDA finds defects in any of the above-mentioned criteria, it may deny approval for the drug, after which (if desired) the sponsor may "ask for a hearing, correct any deficiencies and submit new information, or withdraw the application."[181]

Sponsors may also conduct post marketing clinical trials. As explained above, these are studies conducted after the FDA has approved a drug for marketing.[182] These trials may further confirm or deny the safety of a drug after it has been marketed to the greater public.[183] They also allow companies to study different formulations and dosages of the medication, compare or combine it with other available treatments, and test the drug on different demographics.[184]

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[178] *Id.*
[179] *Id.*
[180] *Id*. at 6–7.
[181] *FDA's Drug Review Process*, U.S. FOOD & DRUG ADMIN. (Nov. 6, 2014), http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm.
[182] *Vaccines, Blood and Biologics, Post Marketing Clinical Trials*, U.S. FOOD & DRUG ADMIN. (Apr. 1, 2011), http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/Phase4Trials/default.htm.
[183] *Id.*
[184] BERT SPILKER, GUIDE TO CLINICAL TRIALS xxii–xxiii (1984), *available at* http://www.virginia.edu/vpr/irb/HSR_docs/CLINICAL_TRIALS_Phases.pdf.

B. Oversight and Enforcement

Technically, the FDA has the ability to inspect ongoing clinical trials and issues sanctions for inaccurate data and fraudulent conduct.

1. Inspections

The FDA begins oversight of clinical trials once a sponsor submits an IND Application.[185] As previously mentioned, once an IND is submitted, the FDA may inspect ongoing trials at any time.[186] However, trials may occur prior to the submission of an IND, and companies completing trials exclusively outside of the United States are not required to submit an IND at all.[187]

2. Disqualifying Data/Study

Overall, if a sponsor follows FDA guidelines, the FDA must accept its data.[188] The FDA has the authority to disqualify data as a result of inspection findings and may also disqualify clinical investigators if there is evidence of deliberate and repeated noncompliance.[189] This remedy is rarely taken though, and may take years to complete.[190] Additionally, the FDA may still accept data that does not conform to its guidelines if it determines the data is "reliable and accurate."[191]

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[185] LEVINSON, *supra* note 11, at 3.
[186] *Id*. at 3.
[187] *Id*.
[188] *See Id.* at 3–4, 35; 21 C.F.R. § 312.120 (providing requirements for accepting data collected abroad without an IND); *see generally* 21 C.F.R. § 312 (providing information about general requirements for drug approval).
[189] 21 C.F.R. § 312.70(a) (2015).
[190] *See FAQs on Debarments/Disqualifications*, U.S. FOOD & DRUG ADMIN. (Aug. 7, 2009), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176043.htm.
[191] *Id.*

C. Additional Protections for Vulnerable Populations in the United States

There are also protections built into the Code of Federal Regulations (C.F.R.) that safeguard clinical trial subjects against certain risks. First, 21 C.F.R. §§ 50.20[192] and 50.25[193] ensures that subjects properly and knowingly consent to participating in clinical trials. Section 50.20 provides: "[N]o investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."[194] "Legally effective informed consent" requires that subjects have a sufficient opportunity to consider their participation.[195] Investigators must minimize the possibility of coercion and undue influence, and information must be given to subjects in a language spoken by them or their representatives.[196] Contracts may not include exculpatory language through which the subject is required to waive or appear to waive any legal rights, or release or appear to release the investigator, sponsor, institution, or its agents from liability for negligence.[197] There may also be additional required safeguards in certain situations to ensure proper consent.[198] For example, participants must be informed of alternative treatment, if available, and must be made aware that they may stop participating at any point.[199]

Section 50.50(D) also provides for greater protections for children, who are considered vulnerable people.[200] It lists factors to explain to volunteers and mandates that if there is more than minimal risk to the child, then the

[192] 21 C.F.R. § 50.20.
[193] *Id.* at § 50.25.
[194] *Id.* at § 50.20.
[195] *Id*.
[196] *Id.*
[197] *Id.*
[198] *Id.* at § 50.25.
[199] *Id.*
[200] 21 C.F.R. § 50.50(D) (2014).

child subjected to testing must also be a direct beneficiary.[201] In other words, the drug tested should be intended for child use, and for a disease, illness, or ailment that the child tested on actually has.

Subpart D of 21 C.F.R. § 56[202] sets up obligations for Institutional Review Boards (IRBs). Prior to an investigation, an IRB must approve the setup.[203] Additionally, the IRB must monitor and ensure that the investigation is conducted in accordance with the approval granted by the board.[204] Certain disclosures are also required (e.g., the disclosure of financial relationships to avoid conflict of interests).[205]

D. Protections for Vulnerable Populations in Foreign Countries

Clinical trials conducted abroad, however, are not held to the same regulations, rules, and standards, and there are also no additional safeguards to ensure vulnerable populations are protected. Prior to 2008, companies conducting clinical trials in other countries were required to follow either the Declaration of Helsinki[206] or the laws of the host country, whichever was stricter or more protective.[207] In 2008, however, the FDA adopted Guidelines for Good Clinical Practices (GCP).[208] These guidelines were derived from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

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[201] *See id.* at § 50.25.
[202] *Id.* at § 56(D).
[203] *Id.* at § 56.103.
[204] *Id.*
[205] *Id.* at § 56.109(g).
[206] *See generally WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects*, WORLD MEDICATION ASS'N, http://www.wma.net/en/30publications/10policies/b3/ (last visited Feb. 23, 2015).
[207] Schmidt, *supra* note 46.
[208] U.S. DEP'T OF HEALTH & HUMAN SERV., GUIDANCE FOR INDUSTRY E6 GOOD CLINICAL PRACTICES: CONSOLIDATED GUIDANCE (1996), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf.

and provide the "standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trials subjects are protected."[209] General principles provided by the document include identifying and weighing risks and benefits and using scientifically sound design and clear, detailed protocol and qualified investigators and medical practitioners.[210] Other general principles include accurate and verifiable recording and reporting, preservation of confidentiality of subjects, "good manufacturing practices," and freely given consent.[211] "Special attention" is also required for trials with "vulnerable subjects."[212] The GCP guidelines are just that, however—guidelines with discretion on enforcement.

The FDA claims that GCPs are necessary to give host countries and other bodies flexibility.[213] It claims that it does not want to place binding resolutions on industries outside of its control.[214] Additionally, the FDA claims that the GCPs are even more protective than the Declaration of Helsinki,[215] and less confusing to other countries and parties who might not know which version of the Declaration is in force.[216] However, this paper will demonstrate that this standard, whether actually more protective than the Declaration of Helsinki or not, still remains inadequate.

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[209] Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 69 Fed. Reg. 32469 (June 10, 2004).
[210] U.S. DEP'T OF HEALTH & HUMAN SERV., *supra* note 208.
[211] *Id*. at 8–9.
[212] *Id*. at 8.
[213] Wilson, *supra* note 60, at 652.
[214] *Id.* at 657.
[215] Schmidt*, supra* note 46.
[216] Wilson, *supra* note 60, at 657.

IV. INADEQUACY OF EXISTING REGULATIONS OF CLINICAL TRIALS CONDUCTED ABROAD AND REMEDIES

While there are a number of regulations in place to protect clinical trial subjects abroad, it is clear that existing safeguards are not enough. First, not all trials conducted abroad are subject to FDA regulation. Second, the regulations themselves are inadequate in that they are not binding and fail to incorporate a number of specific necessary protections.

A. Not All Trials Are Subject to FDA Regulation

One significant challenge the FDA faces in oversight and enforcement of clinical trials is that sponsors conduct many trials, particularly early phase clinical trials, outside of the United States without INDs.[217] Since FDA oversight begins once a sponsor submits an IND, trials conducted before a sponsor submits an IND, or trials where a sponsor chooses not to submit an IND, proceed without the FDA's knowledge and, accordingly, without the FDA's oversight and regulation.[218] Thus, a significant number of trials occur that the FDA has absolutely no knowledge of. The time and money required for an IND incentivize sponsors to begin research without them, and this trend is not only continuing, but increasing.[219] Of course, the FDA cannot see the true ramifications of these trials until years after they are completed, when the sponsor submits an NDA.

B. Inadequate Regulations

Even trials that are subject to FDA regulations lack adequate standards, however. The GCPs are not legally binding, and, furthermore, there are numerous deficiencies in the GCPs themselves. For example, some claim

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[217] LEVINSON, *supra* note 11, at 3.
[218] *Id.* at 17.
[219] *Id.*

that the GCPs focus on efficiency over ethics.[220] Additionally, the guidelines are very general and leave significant room for interpretation.[221] For example, "special protection" and "vulnerable populations" are not clearly defined anywhere in the guidelines. This results in multiple interpretations of the GCPs and thus, a great variability in how they are implemented and how human subjects are protected.[222]

The GCPs also fail to provide multiple important and necessary protections. First, unlike the ICH, there are no detailed or specific protocols for regulating research and obtaining informed consent; in fact there are few protections to assure that proper consent is obtained.[223] For example, there is no language requirement (e.g., that subjects must have access to documents in a/the language they speak). Additionally, the requirements to show patients gave informed consent are much less vigorous than the requirements for trials conducted in the United States.[224] The guidelines only require that companies not coerce or unduly influence a subject, and that the subject should have ample time and opportunity to consider participation and have all of their questions answered. Further, requirements to meet informed consent standards are only a "condition of acceptance for the research."[225] In other words, there are no real penalties for conducting a clinical trial without proper consent, other than the rejection of the data, which is not an issue for big pharmaceutical companies who are conducting numerous clinical trials in multiple countries. Failing to obtain proper consent for one country does not mean that the drug is off track for approval.

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[220] Hirschler, *supra* note 64.
[221] *Id.*
[221] Schmidt, *supra* note 46.
[222] Hearn, *supra* note 84, at 2.
[223] 21 C.F.R. § 50.25 (2014).
[224] Schuman, *supra* note 74, at 134.
[225] *Id.* at 135.

Second, there are no specific requirements to provide additional protection for vulnerable populations. Unlike researchers bound by US requirements, companies conducting clinical trials abroad are not required to follow special rules for trials involving children, and there is no direct benefit requirement.[226] Companies may conduct research for any drug of their choosing even if it does not benefit the subject participants or the host country.[227] They are also free to leave right after the trial without providing medication to the participants, follow-up care, or any guarantee that the subjects could access the drug if it were to be approved in the future.[228]

Third, the GCPs also do not require that drug companies undergo an IRB approval process.[229] Instead, an Independent Ethics Committee (IEC) must "review and approve" a study before it commences.[230] Unlike a drug under an IRB approval process, an IEC is not required to continually review the trials it approves; yearly review is suggested but not mandated.[231] Additionally, like the rest of the GCP guidelines, the definitions for responsibilities of the IEC to ensure the rights and safety of subjects are less precise. Procedures are not clear or specified, thereby lacking "teeth."

A fourth major pitfall of the GCP requirements is that companies and institutions are not required to report trials overseas; there is no mandatory public record, and thus a lack of real transparency.[232] Even the Department of Health and Human Services (HHS) inspector general has raised concerns

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[226] Coyne, *supra* note 52, at 437–38.
[227] NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES (Apr. 30, 2001), https://bioethicsarchive.georgetown.edu/nbac/clinical/execsum.html.
[228] Barlett & Steele, *supra* note 10; Stephens, *supra* note 14.
[229] Mark Cohen, *HHS IG Report Confirms the Rapid Spread of Unregulated Drug Trials Abroad,* GOV'T ACCOUNTABILITY PROJECT (June 22, 2010), http://gaproject.nonprofit soapbox.com/blog/31-2010/622-hhs-ig-report-confirms-the-rapid-spread-of-unregulated-drug-trials-abroad.
[230] Coyne, *supra* note 52, at 439.
[231] *Id.*
[232] Barlett & Steele, *supra* note 10, at 3.

that the "FDA receives minimal information on the performance of foreign institutional review boards . . . [and] has an inadequate database on the people and entities involved in foreign research."[233]

Another problem arises from the GCP guidelines placing compliance burdens on the investigator participating in the trial instead of on the sponsor.[234] Furthermore, guidelines are mostly limited to implementation and maintenance.[235] Pharmaceutical companies are only required to provide a mostly supervisory role, as they can pass most obligations along to the investigators or researchers. Despite their limited responsibilities, pharmaceutical companies are largely the beneficiaries of these trials.

Many pharmaceutical companies argue that standards for all trials conducted are fairly universal throughout the globe. However, even if regulations were equally powerful and binding worldwide, enforcement of these rules is far from universal.[236] In fact, there is virtually no oversight of clinical trials conducted abroad by sponsors in the United States.[237]

C. Challenges in Oversight and Enforcement

Not only are existing regulations inadequate to adequately protect foreign clinical trial subjects, but they are difficult to oversee and enforce. First, FDA inspections of abroad sites are difficult to conduct due to logistical limitations. Second, the legal burden of following rules and regulations is often on the host country, rather than the pharmaceutical company. Third, the few inspections that do occur of abroad sites are often conducted far too late to address any human rights violations. Fourth, data presented to the

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[233] Coyne, *supra* note 52, at 440.
[234] Finnuala Kelleher, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nation*s, 38 COLUM. J.L. & SOC. PROBS. 67, 76 (2004).
[235] *Id.* at 82.
[236] Gardner, *supra* note 119.
[237] Cohen, *supra* note 229.

FDA is limited and non-standardized, and easily skirts FDA disqualification.

1. Logistical Obstacles in Inspections Abroad

While the FDA has the authority to conduct inspections of drug trial sites, it is not required to do so and rarely takes advantage of this authority.[238] Despite the increasing numbers of foreign clinical trials, most inspections are conducted in the United States. The FDA inspects a mere three to four sites per trial, and the majority of those inspections are conducted on US sites.[239] In 2008, the FDA inspected a mere 1.9 percent of domestic clinical trial sites and 0.7 percent of foreign clinical trial cites.[240] Further, the FDA is "16 times more likely to inspect a clinical investigator at a domestic site than a foreign site."[241] One report that reviewed subject enrollment in foreign and domestic sites found that Peru, while boasting the fourth largest subject enrollment, had not received any FDA inspections.[242] Most inspections that do occur happen long after a trial is complete.[243]

According to FDA officials, inspectors are generally only allowed one week to complete inspections, which includes travel time.[244] This short window barely leaves FDA inspectors enough time to travel to foreign countries let alone conduct comprehensive inspections of the site. Additionally, the FDA only has 11 inspectors on staff to conduct foreign inspections.[245] FDA inspectors are generally at the whim of foreign

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[238] Flaherty, *supra* note 35, at 5.
[239] *Id.*
[240] DANIEL R. LEVINSON, DEP'T OF HEALTH AND HUMAN SERV., THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL TRIALS 32 (2007), *available at* http://oig.hhs.gov/oei/reports/oei-01-06-00160.pdf.
[241] LEVINSON, *supra* note 11, at 16.
[242] *Id.* at 15.
[243] Flaherty et al., *supra* note 35, at 5.
[244] LEVINSON, *supra* note 11, at 18.
[245] Flaherty et al., *supra* note 35, at 5.

investigators or institutions to conduct tours of the sites and explain the research being conducted, and host countries frequently supply the translators for inspections done in other countries.[246] Given these limitations, and the fact that inspections generally occur once a test has concluded, FDA inspections usually focus on paperwork: "Were the right forms filed? The right diagnostic tools used? Medical records kept accurately?"[247]

2. Oversight and Enforcement at the Burden of the Host Country

As such, the real oversight and enforcement for trials is in the hands of the host country, which puts the burden of time and money on the investigator. Yet, many countries lack their own oversight and the proper resources and regulatory structure to ensure GCP standards are met.[248] Many of the foreign sites are already understaffed and frequently do not have enough investigators and/or coordinators to conduct proper research, let alone give tours of the site and explain the ongoing trials.[249] In fact, some foreign study-coordinators are responsible for supervising as many as 30 different sites.[250] Additionally, many physicians, researchers, and other staff lack experience conducting clinical trials of the type US sponsors seek to conduct.[251] Foreign officials are not prepared for this burden shift, and the shift is not fair.

On the other hand, there are tremendous financial and economic incentives for the drug sponsors, as well as the host country, researchers,

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[246] *Id*.
[247] *Id*.
[248] *See generally* David Concar, *A Bitter Pill: Exporting Drug Trials to the Developing World,* AMNESTY INT'L MAG. (Summer 2003).
[249] Kelleher, *supra* note 234, at 68, 69; Sandhya Srinivisan, *The Clinical Trial Scenario in India*, WEMOS (Sept. 21, 2009), *available at* http://www.wemos.nl/Eng/wemos_projects_medicines_999_article_the_clinical_trial_scenario_in_india.htm.
[250] Wilson, *supra* note 60, at 660.
[251] *Id*. at 660, 663, 668–69; LEVINSON, *supra* note 11, at 7.

and doctors, to have clinical trials that result in drug approval. There is a lucrative market for drug applications and, as shown above, a lot of profit to be made in the pharmaceutical industry from new medication. In many unindustrialized countries, there is a severe lack of functioning health care systems, but enormous financial incentives for investigators and doctors to participate in the clinical trial. Foreign IECs and IRBs are also frequently less experienced and have similar financial incentives should the trial succeed. Many for-profit companies have popped up "to sell their ethical review services to the highest bidder."[252] There is no real threat of audits or oversight, so workers on site can give an incredibly incomplete picture of what is actually occurring in the trial, and foreign trials have the potential to yield high "positive" results. Thus, there is no assurance that the FDA has any real picture of what is actually occurring in FDA-regulated trials.

3. Inspections Late in the Game

The high cost of visas, translators, and transportation certainly makes foreign inspections less appealing than those in the United States. This is probably why the review that rarely does occur, happens very late in the game.[253] Of the few inspections the FDA makes, most occur after the FDA receives a marketing application from a sponsor, as opposed to when a clinical trial is ongoing, and most are focused on verifying the accuracy of the data.[254] For example, a South African center violated FDA regulations, but citations were not issued until two years after the violations occurred.[255] In Romania, a researcher died three years before the center even received a citation.[256] In an interview conducted by Chris Hansen of Dateline NBC, former FDA Commissioner Dr. David Kessler expressed fear about the

[252] Hearn, *supra* note 84, at 1.
[253] Flaherty et al., *supra* note 35, at 5.
[254] LEVINSON, *supra* note 11, at 4.
[255] Flaherty et al., *supra* note 35, at 5.
[256] *Id.*

risks regarding clinical trials and the FDA's ability to regulate and monitor these trials:

"'What's going to happen, and I can predict this . . . it's been the history over the last 100 years. We don't act until there's a problem.'

'Until people die?' Hansen asked.

'Regrettably.'"[257]

In fact, David A. Lepay, the FDA's director of investigations, estimated that over 90 percent of clinical trials done overseas are not reported in advance to the FDA.[258] This just further reiterated that the FDA has no knowledge of what is going on in these trials abroad.

4. Non-Standardized Data

Additionally, there is no fixed standard format for data submission. Data is often presented inconsistently, "making it difficult to locate [needed] clinical trial information," and sponsors frequently fail to provide important information in their reports, including site location and subject enrollment.[259] Additionally, sponsors usually submit clinical study reports in "portable document formats" (PDFs), which the FDA may not analyze directly.[260] In a report completed by the Office of the Inspector General, the FDA could not provide detailed clinical trial data for over 20 percent of the applications the agency sought to review.[261] And, the FDA was unable to locate *any portion* of virtually one-third of those incomplete applications.[262] Of the final applications found, some applications were in paper form and some were in electronic form, and in many of them sponsors failed to

[257] Sandler, *supra* note 39.
[258] Flaherty et al., *supra* note 35, at 5.
[259] LEVINSON, *supra* note 11, at 19.
[260] *Id.*
[261] *Id.*
[262] *Id.*

include site locations and subject enrollment.[263] This practice would have been completely unacceptable in the United States, yet neither the FDA nor the pharmaceutical companies at fault have presented a remedy to account for this completely missing information.

D. Potential Avenues for Relief Fall Short

Currently, means for enforcement are limited and avenues of relief for individuals wronged by clinical trials are few and far between. To begin, FDA remedies offer little more than a slap on the wrist to companies who violate regulations or laws. Additionally, there are few methods for individuals harmed to bring suit against foreign pharmaceutical companies.

1. FDA Remedies

The FDA has the authority to enforce an IND through injunctions and criminal prosecutions; however, this action is rarely taken.[264] To make matters worse, should a sponsor or investigator violate GCP guidelines, there are no penalties other than rejection of their data, which the FDA will still examine even though it will not accept it.[265] In other words, the FDA would not do anything to punish unethical researchers; it would only disqualify their data.[266] Additionally, even if a sponsor's conduct injures or kills a subject, FDA regulations do not require that the sponsor "administer post-trial care, compensate participants, or in the event of death, compensate the participant's family."[267]

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[263] *Id.*
[264] 21 U.S.C. §§ 331(e)–333 (2012).
[265] Schuman, *supra* note 74, at 135.
[266] Wilson, *supra* note 60, at 660.
[267] Stacey B. Lee, *Informed Consent: Enforcing Pharmaceutical Companies' Obligations Abroad*, 12 HEALTH & HUM. RTS. J. 15, 23 (2010), *available at* http://www.hhrjournal.org/wp-content/uploads/sites/13/2013/07/4-Lee.pdf.

2. International Covenant on Civil and Political Rights (ICCPR)

In 1966, the United Nations (UN) incorporated the concept of informed consent into the ICCPR as a human right. Article 7 states that "no one shall be subjected without his free consent to medical or scientific experimentation."[268] However, the ICCPR, while conferring absolute rights, is not self-executing. It has not yet been applied in a human rights lawsuit against a state actor and does not create a binding legal obligation enforceable in federal court. Thus, clinical trial subjects abroad cannot use the ICCPR as a legal document to file suit against pharmaceutical companies in the United States.[269]

3. Alien Tort Statute

The Alien Tort Statute (ATS) (28 U.S.C. § 1350) states "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."[270] Action under the ATS, however, is very limited. The only ATS case the US Supreme Court has ruled on is *Sosa v. Alvarez Machain.* In *Sosa,* the court held that the ATS was "intended only to prohibit conduct for a moderate number of new international law violations that were sufficiently 'specific, universal and obligatory.'"[271]

Following the Trovan experiments, discussed at the beginning of this paper, families of the dead and injured children realized they had few avenues for relief aside from the ATS. They filed suit against the pharmaceutical company Pfizer under the ATS for violating "a norm of customary international law prohibiting medical experimentation on non-

[268] *See* Abdullahi v. Pfizer, Inc., 562 F.3d 163, 175 (2d Cir. 2009).
[269] *See id.* at 180.
[270] 28 U.S.C. § 1350 (2014).
[271] Samantha Evans, *The Globalization of Drug Testing: Enforcing Informed Consent Through the Alien Tort Claims Act*, 19 TEMP. INT'L & COMP. L.J. 477, 483 (2005) (quoting Sosa v. Alvarez-Machain, 542 U.S. 692, 732 (2004)).

consenting human subjects."[272] Their claim was initially dismissed by the district court, but on appeal, the Second Circuit reversed. The appellate court explained that, in considering whether an international norm is sufficient to bring a cause of action under the ATS, the court must examine whether the norm is accepted by the international community and whether states universally abide by the norm out of a "sense of mutual concern."[273] Additionally a court must examine current norms compared with eighteenth century paradigms in place when the ATS was first enacted.[274] The court found that nonconsensual drug trials, thus, violated customary international law.[275] Pfizer subsequently filed a writ of certiorari, but the Supreme Court denied the writ, thereby declining to hear the case.[276]

While the Pfizer case may bring hope to those injured by improperly conducted clinical trials, it is difficult to say how far, if anywhere, the holding may actually reach. *Sosa v. Alvarez-Machain*[277] seems to leave very little of the statute for potential plaintiffs to work with.[278] Thus, while a lawsuit was successful for one plaintiff, there is no indication that it would be successful again. Because the Supreme Court has yet to interpret whether the ATS applies to pharmaceutical companies conducting trials abroad, it is very difficult to predict how a court might rule on a case similar to Pfizer.

4. Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act (FCPA) makes it illegal to offer or make corrupt payments to foreign officials for the purpose of securing or

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[272] *Abdullahi*, 562 F.3d at 194.
[273] *Id*. at 185.
[274] *Id.*
[275] *Id.* at 169.
[276] *Id.* at 163.
[277] Sosa v. Alvarez*,* 542 U.S. 692, 692 (2004).
[278] Anton Metlitsky, C*ommentary: What's Left of the Alien Tort Statute?,* SCOTUSBLOG (Apr. 18, 2013, 10:06 AM), http://www.scotusblog.com/2013/04/commentary-whats-left-of-the-alien-tort-statute/.

retaining business.[279] Critics of pharmaceutical company activities in developing nations have more recently relied on the use of this statute to punish human rights violators. In 2009, Assistant Attorney General Lanny Breuer warned, the Department of Justice will be "intensely focused on rooting out foreign bribery in [the pharmaceutical] industry[.]"[280] Additionally, the law is defined now such that any government employee may be considered a foreign official; generally anyone working for a public healthcare system may be subject to the Act.[281]

Thus, the FCPA is certainly a meaningful avenue for relief. However, it is limited to punishing employees who make or receive corrupt payments. While pharmaceutical companies and sponsors may be held accountable for corrupt exchange of money, there are no protections for individuals who were not properly informed of the risks of the trial or did not give adequate consent.[282] Additionally, of course, the Act fails to solve the underlying issue. It is not until *after* a subject is severely injured or dies that the lawsuit will take place. Litigation is definitely a powerful avenue for relief, but it is usually the least preferable method when discussing human rights abuses.

5. Foreign Lawsuits

Although host countries may be able to file suit against drug trial sponsors, injured citizens are not assured any direct benefit from such lawsuits. Developing nations may not even have the resources to bring suit in the first place. The outcome of any such suit also has serious underlying ethical problems. For example, the government of Nigeria sued Pfizer in

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[279] William Jordan & Jason Popp, *Mitigating FCPA Risks in Clinical Trials Conducted Abroad*, PHARM. COMPLIANCE MONITOR (Nov. 26, 2012), http://www.pharmacompliancemonitor.com/mitigating-fcpa-risks-in-clinical-trials-conducted-abroad/3579/.

[280] *Id.* (alteration in original).

[281] *Id.*

[282] MICHAEL SEITZINGER, FOREIGN CORRUPT PRACTICES ACT (FCPA): CONGRESSIONAL INTEREST AND EXECUTIVE ENFORCEMENT (Feb. 7, 2012), https://www.fas.org/sgp/crs/misc/R41466.pdf.

Nigerian Federal High Court claiming the company never "obtained approval of the relevant regulatory agencies . . . nor did the defendant seek or receive approval to conduct any clinical trial at any time before their illegal conduct[.]"[283] In 2009, Pfizer settled with its 200 plaintiffs out of court for $75 million.[284] This case raised serious ethical concerns. First, according to a leaked US embassy cable, Pfizer hired investigators to unearth evidence of corruption against the Nigerian attorney general to persuade him to drop charges against the company.[285] Second, interestingly, a few months after the settlement, the medical records of the victims could "not be found" at either the Kano State Ministry of Health or at the Infectious Diseases Hospital where the clinical trials were conducted.[286]

V. MEANINGFUL SOLUTIONS

Neglecting foreign nations is far too easy, despite the strong presence of US companies in those countries. US companies should have the same standards for treatment, regardless of where a human subject resides; citizens of other countries deserve the same protections that citizens of this country are guaranteed.

In case international human rights are not enough of an incentive to induce action, let us not forget the significant number of pharmaceutical drugs that have *already* been approved for market in the United States primarily, or entirely, as a result of clinical trials conducted in other

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[283] James Sturcke, *Nigeria Sues Pfizer for $7bn over Drug Tests*, THE GUARDIAN, June 5, 2007, http://www.theguardian.com/world/2007/jun/05/health.healthandwellbeing.
[284] Joe Stephens, *Pfizer to Pay $75 Million to Settle Nigerian Trovan Drug-Testing Suit*, WASH. POST, July 31, 2009, http://www.washingtonpost.com/wp-dyn/content/article/2009/07/30/AR2009073001847.html.
[285] Sarah Boseley, *WikiLeaks Cables: Pfizer 'Used Dirty Tricks to Avoid Clinical Trial Payout,'* THE GUARDIAN, Dec. 9, 2010, 16:33, http://www.theguardian.com/business/2010/dec/09/wikileaks-cables-pfizer-nigeria.
[286] Auwalu Umar, *Nigeria: Pfizer-Victims' Medical Records Missing*, DAILY TRUST, Oct. 5, 2009, http://allafrica.com/stories/200910050887.html.

countries. Experiments conducted under current regulations not only have severely harmed citizens abroad, but also have had dire consequences for citizens in our own country. For example, not only did the Trovan experiment lead to a number of deaths and disabling conditions for Nigerian children, but within the first 16 months of its approval, there were also 140 reports of liver problems, at least 14 reports of liver failure, and six deaths in the United States.[287] Clinical trials present an incredible method to facilitate drug innovation and lifesaving cures. However, the current beneficiaries of these trials are mostly pharmaceutical companies. The risk of these experiments should instead be just as great for drug sponsors as it is for drug trial participants, if not greater. A number of mechanisms could reduce the number of, and potential for, unethical and dangerous clinical trials.

A. Binding Regulations

There are a number of regulations that should be enacted to adequately protect the human rights of individual subjects in US clinical trials conducted abroad. To begin, the standards for trials conducted abroad should be just as stringent and protective as those conducted in the United States. Additionally, all trials conducted should be published in a public registry and database, and data should be standardized. Inspections should be targeted and more frequent, and regulatory US agencies should develop stronger and closer relationships with host countries. Lastly, subjects tested on should receive some form of benefit from the trial and its results.

1. US Standards

First, at the very minimum, pharmaceutical companies conducting research in foreign countries ought to be subject to the same minimum

[287] Stephens, *supra* note 14, at 5.

standards as if they were conducting the trials in the United States. This would require companies to submit an IND and secure approval from an IRB. Additionally, companies would be held to the same requirements of 21 C.F.R. § 50, which provides specific requirements for obtaining consent, and additional safeguards for children in clinical investigations.[288]

All sponsors should be subject to FDA regulation to ensure proper oversight and remedies. An IND requirement first ensures that the FDA is aware of all trials currently being conducted. Second, it would require that clinical trials be approved by an IRB.[289] IRBs have more stringent approval and oversight requirements than IECs. The standards IRBs must meet are also more clear and comprehensive. Third, the IND requirement would ensure that sponsors are held to the same informed consent standards. For example, sponsors would be required to provide information in the participants' language of choice and disclose their methods of obtaining consent. Informed consent is especially vital with vulnerable populations. Subjects must understand the nature of the experiment they are participating in, the risks and potential benefits of the experiment, and the reality of aftercare treatment once the experiment is over. No company should ever be allowed to conduct an experiment without explaining its ramifications to a subject in a language they speak. Such a violation would be unimaginable in the United States and this conduct should not be permitted by US companies regardless of where the conduct occurs. Finally, this requirement would allow the FDA to enforce the approved IND through injunctions and/or criminal prosecutions (versus simply rejecting data).[290] This would deter at least some fraud and abuse in the clinical trial because

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[288] 21 C.F.R. §§ 50.1–50.56 (2013).
[289] COUNCIL FOR INT'L ORGS. OF MED. SCIENCES, INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS 17–18 (2002), *available at* http://www.cioms.ch/publications/layout_guide2002.pdf.
[290] *See* 21 U.S.C. §§ 331(e)–333 (2013).

consequences for violating the rules and regulations are more than just a slap on the wrist.

2. Mandatory Public Registry

The FDA should also require registration for all clinical trials, regardless of the success of the trial and country in which the trial takes place. Trials that were not reported should no longer be accepted in the approval process for drugs. Prior to 2007, reporting was voluntary unless the trial was conducted (1) to test the effectiveness of experimental treatments for (2) "*serious* or *life-threatening* diseases or conditions" (3) under the "FDA's Investigational New Drug (IND) regulations."[291] This regulation limited reporting requirements in three major ways—exempting most trials conducted abroad from this reporting requirement.[292] In 2007, Congress expanded the scope of applicable clinical trials and informational requirements for mandatory FDA reporting by enacting the Food and Drug Administration Amendments Act (FDAAA).[293] However, numerous questions remain as to how the FDAAA applies to foreign trials.[294] Without mandatory reporting, companies are incentivized to self-select which clinical trials (i.e., the successful ones) to report, resulting in incomplete and biased views of the results.[295] Also, without mandatory reporting, if a company holds unethical or dangerous trials that are unsuccessful, the company may just choose to not submit those trials as part of an IND or drug marketing application. A public registry requirement for all trials

[291] Carolyn R. Hathaway et al., *The Web of Clinical Trial Registration Obligations: Have Foreign Clinical Trials Been Caught?,* 64 FOOD & DRUG L.J. 261, 262 (2009) (emphasis in original).
[292] *Id.*
[293] *Id.* at 263–66.
[294] *Id.* at 269.
[295] WORLD HEALTH ORG. (WHO), INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM (ICTRP), REPORTING OF FINDINGS OF CLINICAL TRIALS (2011), *available at* http://www.who.int/ictrp/results/en/.

would ideally provide for more objective and comprehensive data collecting. It would hold companies more accountable in ensuring their clinical trials were conducted ethically, both to the public and to oversight organizations. A public registry would allow the public and media to more easily examine these trials, demanding change and using the market as a strategy for punishment when necessary and as a deterrent. The registry would also give oversight committees more information for approval. In analyzing whether a drug should be approved or not, the FDA would have all of the necessary data to make a truly informed decision. It would have access to more than just the trials a drug company deems relevant.

3. Standardized Electronic Trial Data and an Internal Database (for the FDA)

The mandatory reports should be standardized and in electronic form to ensure that any potential viewers always have the most current data available to effectively analyze them. This would help the FDA conduct trend analysis, identify sites and sponsors that pose the most risks, and form a comprehensive database of trial sites where there are adverse events or that have histories of noncompliance.[296] Pharmaceutical companies might argue that additional oversight will cost more time and money to the agency or regulatory bodies, but standardized data would allow for better, quicker, and more efficient review. This method helps to ensure that the drug sponsor will be the entity to incur any additional costs. This would also prevent situations like that in Kano, where all records of the individuals participating in the trial magically "disappeared."

4. More Efficient Inspections

The FDA is currently developing a computer-based program referred to as a "site selection tool" in order to maximize resources in clinical trials.

[296] LEVINSON, *supra* note 11, at 20.

This would allow the FDA to select sites for inspection based on specific risk factors.[297] The FDA should continue development of this software, as well as look at other methods of oversight to determine which trials pose the most risks to host country subjects. This would not prevent companies from conducting necessary trials in the most risk-prevalent countries, but rather would increase oversight of these trials to ensure the subjects remain protected.

5. Foster Relationships with Host Countries

Additionally, the FDA should work more closely to foster relationships with foreign regulatory bodies and governments. If officials worked together to create an international registry or database to share results of inspections and keep each other up to date, the FDA could better maximize its resources, as well as give governments additional incentive to protect their individual citizens. Getting all governmental bodies on the same page would also send the message that compliance with these regulations is important and enforcement is a real threat.

6. Increase Inspection Frequency and Funding

The FDA should also inspect more clinical trials in more countries. It should pay specific attention to trials conducted by companies who have falsified data or violated standards in the past, as well as countries especially vulnerable and/or susceptible to corruption or abuse in research. This mechanism may be costly and resource consuming. Thus, pharmaceutical companies should be required to pay for onsite inspections conducted by the FDA, similar to the Prescription Drug User Fee Act

[297] *Id.* at 20–21.

(PDUFA).[298] PDUFA authorizes the FDA to collect fees from drug manufacturers to support the drug approval process.[299] The FDA could increase these fees—which currently account for roughly one-quarter of the agency's spending—to allow for better enforcement and to ensure the burden, again, is on the drug sponsor.[300] The FDA could also reconsider the current allocation of funds collected and re-examine the most effective and efficient method to use the fees being generated to ensure ethical, safe, and accurate clinical trials.

7. Benefits Requirement

Additionally, companies conducting research abroad should have new required benefits. Currently, if sponsors complete testing on children in the United States, they must go through three levels of approval. Clinical trials may proceed, first, if the IRB finds that there is no greater than minimal risk to the children. If there is greater than minimal risk, the risk must be justified by the anticipated benefit to the subjects. Investigators must show that the "relation of the anticipated benefit . . . is at least as favorable to the subjects as that presented by available alternative approaches; and . . . [a]dequate provisions are made for soliciting the assent of the children and permission of their parents or guardians[.]"[301] Additionally, investigators generally must show that the same research could not be carried out on less vulnerable subjects and that subjects will be "assured reasonable access to any diagnostic, preventative or therapeutic products that become available

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[298] Steven W. Postal & Robyn Whipple Diaz, *A Remedy in Sight: International Clinical Research Regulation in the Wake of Guatemala and Nigeria*, 6 PITT. J. ENVTL. L. & PUB. HEALTH L. 1, 30 (2011).
[299] 21 U.S.C. § 379h (2012).
[300] Gail Dutton, *2011 Budget Outlook: Trim, Cut, Then Slash,* GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Feb. 7, 2011, http://www.genengnews.com/analysis-and-insight/2011-budget-outlook-trim-cut-then-slash/77899360/.
[301] 21 C.F.R. § 50.52 (2013).

as a consequence of the research."[302] There are also very strict requirements for obtaining consent by parents and guardians.[303]

There are some exceptions to these general requirements (for example, if the procedure or intervention will likely yield generalizable knowledge about the subjects' disorder that is of vital importance to understanding it), but these exceptions are still severely limited and still require some sort of benefit to the subject.[304] These requirements should extend to any participant in another country. In other words, companies would be required to show that the host country would benefit directly from the drug trial conducted any time the trial poses more than a minimal risk. There is a similar benefit assurance guideline in the International Ethical Guidelines for Biomedical Research involving Human Subjects.[305] Additionally, post-trial treatment, if effective, should be provided to the subjects of the clinical trial upon drug approval (should the subjects desire it). While a drug company cannot ensure that a foreign country will approve marketing or sell the pharmaceutical, there should at the very least be follow-up care provided for drug trial subjects.

B. Stricter Enforcement and Sanctions

As previously mentioned, all sponsors should be required to submit an IND and be under FDA supervision. Sponsors should be held accountable for any violations instead of simply having their data disqualified. In addition, governments should also work together to create an international tribunal that has the authority to police trials, similar to the UN or World Health Organization. For drug companies to participate in clinical trials in

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[302] COUNCIL FOR INT'L ORGS. OF MED. SCIENCES, *supra* note 289, at 64. The guidelines also suggest additional protections for vulnerable patients such as minorities, those in poverty, prisoners, etc. *Id.*
[303] 21 C.F.R. § 50.55 (2013).
[304] 21 C.F.R. § 50.54 (2013).
[305] COUNCIL FOR INT'L ORGS. OF MED. SCIENCES, *supra* note 289, at 64.

those countries, participating in the tribunal for resolving disputes would be mandatory. This would further enforce the message that institutions are to follow certain standards when conducting clinical trials and assure companies that there are sincere threats of oversight and consequences for violations. Additionally, countries could draw on trade-related aspects of international property rights. For example, they could deny intellectual property protections to drug companies who have developed drugs through trials that violated rights of participants. This would also alleviate pharmaceutical company concerns that the United States is being paternalistic. A tribunal would give countries an opportunity to work together to achieve common goals.

CONCLUSION

Clinical trials are a critical part of drug development. They are an integral step in defeating illness, preventing pandemics, and finding cures to diseases, chronic illnesses, and detrimental conditions. However, the potential benefits of clinical research must not be completely offset by the costs. Subjects of clinical trials conducted abroad are especially susceptible to exploitation and it is imperative that clinical trial sponsors, not the participants or regulators, feel the brunt of these burdens. Human lives should never be sacrificed for money.

History has demonstrated the importance of proper regulation of clinical trials. While research may save lives, it should not be at the cost of others' lives. It is vital that subjects risking their entire future understand the full risks of their participation, and that they have the assurance that they can trust the process. Properly conducted trials are essential for participants, as well as future users of the medication. How many more lives are we willing to lose to pharmaceutical profits?