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Table of Contents

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INTRODUCTION

In 2010, American President Barack Obama issued a personal apology to the people of Guatemala for a clinical trial that occurred over 60 years ago.[1] The White House issued the apology after Professor Susan M. Reverby revealed that the United States Public Health Service infected vulnerable Guatemalans with venereal diseases without their consent in the 1940s.[2] More than a thousand people were targeted, including women living in an asylum for the insane, prostitutes, and prisoners.[3] The methods used to infect these unwitting human research subjects were horrific: syphilis was injected via the skull into epileptic women; gonorrhea was administered via a woman's eyes; and syphilis bacteria were applied to prisoners' previously scraped faces when attempts at regular exposure were unsuccessful.[4] The trials ultimately left 83 people dead.[5]

The revelations of the Guatemalan trials reminded the world, once again, of the potential for serious human rights violations in the course of a clinical trial. The Nazis' medical experiments during World War II, the Tuskegee syphilis study, and the Guatemalan trials all demonstrate the likelihood of serious harm when medical testing is conducted on vulnerable human subjects without impartial review and oversight.[6] Unfortunately, the lessons from these three notorious incidents have not been applied to the modern clinical trials industry where trials are run overseas—sometimes in

[1] Jake Tapper, *President Obama Apologizes to Guatemalan President for "Shocking," "Tragic," "Reprehensible" Syphilis Study*, ABC NEWS (Oct. 1, 2010), http://blogs.abcnews.com/politicalpunch/2010/10/president-obama-apologizes-to-guatemalan-president-for-shocking-tragic-reprehensible-syphilis-study.html.

[2] Susan Reverby, *Ethical Failures and History Lessons: The U.S. Public Health Service Research Studies in Tuskegee and Guatemala*, 34 PUB. HEALTH REV. 1 (2013). *See also* Glenn Cohen & Eli Y. Adashi, *In the Wake of Guatemala: The Case for Voluntary Compensation and Remediation*, 102 AM. J. PUB. HEALTH 4, 4 (2011).

[3] Ryan Jaslow, *Guatemala Syphilis Experiments in 1940s Called "Chillingly Egregious*," CBS NEWS (Aug. 31, 2011, 11:33 AM), http://www.cbsnews.com/news/guatemala-syphilis-experiments-in-1940s-called-chillingly-egregious/. *See also* Tapper, *supra* note 1.

[4] Jaslow, *supra* note 3. *See also* Tapper, *supra* note 1.

[5] Jaslow, *supra* note 3.

[6] *See U.S. Public Health Service, infra* note 18 (discussing related historical events).

third-world countries—by secretive contract research organizations (CROs),[7] which are capable of evading impartial review by the United States Food and Drug Administration (FDA).

In his apology, President Obama "reaffirmed the United States' unwavering commitment to ensure that all human medical studies conducted today meet exacting United States and international legal and ethical standards."[8] Yet, as this article demonstrates, current federal oversight of foreign clinical trials is severely lacking. Seldom do these trials receive on-site compliance inspections from the FDA despite the fact that they are often being run to produce data for a New Drug Application, which the FDA reviews before approving a drug for American patients. In recent years, not only have trials been sent abroad, they have also been commercialized, with the aforementioned CROs running trials for pharmaceutical companies (hereinafter pharmaceutical sponsors). The dangers of the FDA's inability to inspect the large number of trials being sent overseas have been exacerbated by this new model of clinical testing. For the FDA to ensure that both the rights of the human subjects are being protected and that the data yielded in these clinical trials are valid, it will need to reformulate its regulatory strategy to adjust to the paradigm shift in the way today's clinical trials are run.

This article addresses the barriers to FDA oversight with the rise of commercialized foreign clinical trials. Part I provides an overview of the FDA's clinical trial regulations. In doing so, this article illustrates how the standards for accepting foreign clinical trial data were developed when clinical trials were largely run in the United States. Part I also traces the rise of CROs and explores how they contributed to the outsourcing of clinical trials. Part II examines the FDA's three criteria for approving foreign clinical trial data. Here, the article discusses the FDA's attempts to ensure that foreign data are applicable to the American population and then analyzes the FDA's regulations regarding clinical investigators. In this section, CRO liability is examined, because CROs are now the primary orchestrators of clinical trials abroad. The FDA's inability to inspect such clinical trials fully is then discussed. Part III focuses on the federal government's inability to take appropriate enforcement actions in this area. Part IV explains why the internationalization of Good Clinical Practices via the International Conference of Harmonization is not an adequate substitute for FDA regulation and oversight. Then the article briefly summarizes the FDA's attempts at improving its foreign clinical trial oversight. Finally, the article makes several brief recommendations for Congress.

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[7] Contract research organizations are also referred to as "clinical research organizations."

[8] *See* Office of the Press Secretary, *Read-*Out *of the President's Call with Guatemalan President Colom*, THE WHITE HOUSE (Oct. 1, 2010), http://www.whitehouse.gov/the-press-office/2010/10/01/read-out-presidents-call-with-guatemalan-president-colom.

This article focuses primarily on the testing of drugs, as opposed to biologics and medical devices, unless otherwise noted.

I. THE FDA'S STANDARDS FOR CLINICAL TRIALS WERE PRIMARILY DEVELOPED BEFORE TRIALS WERE SENT OVERSEAS AND RUN BY CONTRACT RESEARCH ORGANIZATIONS

In this part, the history of clinical trial regulations in the United States and the recent phenomenon of the commercialization of overseas clinical trials are explored.

Congress first addressed clinical trials in the 1930s, but it was not until the 1960s that clinical trial conduct and foreign clinical trial data were reviewed. The Food, Drug, and Cosmetic Act of 1938 (FDCA)[9] requires that "new investigational drugs … undergo clinical trials on human subjects" to show that they are both safe and effective before being sold in the United States.[10] In 1962, the FDA notified pharmaceutical sponsors that foreign clinical trial data would be accepted but only in addition to domestic data that established that a drug was safe and effective.[11] That same year, in the Drug Amendments of 1962, Congress mandated "that any IND [i.e., Investigational New Drug] be conditioned upon informed consent by human subjects."[12] Thus, in 1963, the FDA began to oversee "the conduct of clinical studies involving FDA regulated products."[13]

Starting in the 1970s, the FDA promulgated the regulations for the conduct of clinical trials that are still in effect today.[14] In 1975, the FDA put forth regulations establishing that foreign clinical trial data would be considered equivalent to domestic trial data[15] supporting a new drug application, provided that the Declaration of Helsinki's ethical guidelines[16]

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[9] 21 U.S.C. § 301 (2012).

[10] Daniel R. Levinson, *Challenges to the FDA's Ability to Monitor and Inspect Foreign Clinical Trials*, DEP'T. HEALTH & HUMAN SERV. 1 (June 2010), http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf (hereinafter 2010 HHS IG REPORT).

[11] William DuBois, *New Drug Research, The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT'L L. 161, 190 (2003).

[12] FOOD AND DRUG LAW: CASES AND MATERIALS 634 (Peter Barton Hutt et al. eds., 3d ed. 2007).

[13] U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, PROGRAM 7348.811, CHAPTER 48–BIORESEARCH MONITORING CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS Part I, 2 (Dec. 2008), http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf.

[14] U.S. FOOD & DRUG ADMIN., CLINICAL TRIALS AND HUMAN SUBJECT PROTECTION, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm (last updated Dec. 18, 2015).

[15] International Clinical Research Standards; Acceptance of Foreign Data, 40 Fed. Reg. 16053 (Apr. 9, 1975) (codified at 21 C.F.R. pt. 312).

[16] *See World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, WORLD MED. ASS'N 1(1964), http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC20-Attach-1.pdf (adopted in 1964). "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over

were met.[17] Only a few years before the FDA loosened its requirements for foreign clinical trial results did the American public become aware of ethical violations in human subjects testing that occurred in the United States.

In 1972, the Associated Press exposed the United States Public Health Service and the Tuskegee Institute's unethical experiments on impoverished black men with syphilis.[18] The men were not given access to penicillin, even after it became known that it was the cure for the disease.[19] In response, Congress passed the 1974 National Research Act that led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which produced the *Belmont Report*.[20] The *Belmont Report* begins with a synopsis of the Nuremberg Code, written during the Nuremberg War Crime Trials that implicated Nazi scientists who had experimented on concentration camp prisoners during World War II.[21] The report's authors argued that the Nuremberg Code's rules were "inadequate" to deal with clinical trials in a post-war era and "broader ethical principles" were needed.[22] The *Belmont Report* then listed the essential "ethical principles" of human subject research, which included making sure that human "subjects enter into the research voluntarily and with adequate information," "minimiz[ing] possible harms" to the subjects, and ensuring that there are "fair procedures and outcomes in the selection of research subjects."[23] In 1981, the Department of Health and Human Services (HHS) and the FDA modified "and made as compatible as possible under their respective statutory authorities, their existing human subjects regulations."[24] It was also around this time

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the interests of science and society". *Id.* Among other things, the Declaration has guidelines on informed consent, testing on vulnerable populations, and the qualifications of clinical investigators. *Id.* at 2-5. Since then, the FDA has revised its regulations as the Declaration has been updated. U.S. FOOD & DRUG ADMIN. GUIDANCE FOR INDUSTRY—ACCEPTANCE OF FOREIGN CLINICAL STUDIES, 2 (Mar. 2001), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm124939.pdf; *see generally* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF—FDA ACCEPTANCE OF FOREIGN CLINICAL STUDIES NOT CONDUCTED UNDER AN IND FREQUENTLY ASKED QUESTIONS 2-15 (Mar. 2012), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf.

[17] FOOD AND DRUG LAW, *supra* note 12, at 650.

[18] CTR. FOR DISEASE CONTROL & PREVENTION, U.S. PUBLIC HEALTH SERVICE SYPHILIS STUDY AT TUSKEGEE, http://www.cdc.gov/tuskegee/timeline.htm (last visited Apr. 11, 2016).

[19] *Id.*

[20] Adam H. Laughton, *Somewhere to Run, Somewhere to Hide?: International Regulation of Human Subject Experimentation*, 18 DUKE J. COMP. & INT'L L. 181, 187 (2007).

[21] U.S. DEP'T OF HEALTH & HUMAN SERV., THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (Apr. 18, 1979), http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html.

[22] *Id.*

[23] THE BELMONT REPORT, *supra* note 21, (expressing concerns about vulnerable populations being singled out, in particular "racial minorities, the economically disadvantaged, the very sick, and the institutionalized. …" at Part C, 3.

[24] U.S. DEP'T OF HEALTH & HUMAN SERV., FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS ("COMMON RULE"), http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html (last visited Apr. 7, 2016).

that the FDA began the Bioresearch Monitoring Program (BIMO) to implement guidance "for inspections of clinical investigators, sponsors, and IRBs [Institutional Review Boards],"[25] and by the late 1980s, regulations regarding sponsors, monitors, and clinical investigators were put into place.[26]

At the start of the 1990s, the FDA's clinical trial regulations were still evolving. In 1991, the Federal Policy for the Protection of Human Subjects, also known as the Common Rule, was implemented, and the FDA subsequently codified it.[27] The Common Rule summarizes the regulations for informed consent, assurances of compliance, and IRBs.[28]

However, in the mid-1990s, clinical trials started being outsourced overseas. One survey found that from 1995 to 2005, there was a decline in the number of trials in Western Europe and the United States, whereas "the number of countries serving as trial sites outside the United States more than doubled."[29] By 2008, an HHS Office of Inspector General (OIG) report found "80% of approved marketing applications for drugs and biologics" included data from overseas trials, with the number only expected to rise as the market becomes more globalized.[30] Moreover, the FDA does not see the results of all clinical trials, and not all clinical trials are appropriately registered.[31] The HHS report also found that more than half of all human subjects taking part in trials were at foreign clinical trial sites and that foreign clinical trial sites made up more than half of "all trial sites in marketing applications for drugs."[32] Although the FDA's regulations regarding clinical trials have been modified repeatedly through the years, the FDA has not updated its regulations to reflect this new overseas trend in an adequate manner.

A. Why Clinical Trials Have Gone Overseas

There are several reasons why many clinical trials are run overseas today—some more well-known than others. The most publicized explanations for why pharmaceutical sponsors have increasingly moved their testing

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[25] 2010 HHS IG REPORT, *supra* note 10, at 4.

[26] COMPLIANCE PROGRAM GUIDANCE MANUAL, *supra* note 13, at 2 (stating "[21 CFR Parts 312, 314, 511, and 514] were published on March 19, 1987, and became effective on June 17, 1987").

[27] *See* U.S. DEP'T OF HEALTH & HUMAN SERV., *supra* note 24.

[28] *Id.*

[29] Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816, 816 (2009).

[30] 2010 HHS IG REPORT, *supra* note 10, at ii.

[31] Adriana Petryna, *Clinical Trials Offshored: On Private Sector Science and Public Health*, 2 J. BIOSOCIETIES 21, 31 (2007). *But see* Ida Sim & Don Detmer, *Beyond Trial Registration: A Global Trial Bank for Clinical Trial Reporting*, 2 J. PLOS MED. 1090, 1090 (2005) (noting that even after the FDA Modernization Act of 1997 went into effect, stipulating that all clinical trials involving treatments for life-threatening conditions and diseases be submitted to the National Institutes of Health's ClinicalTrials.gov, fewer than half of the commercially run trials were being registered).

[32] 2010 HHS IG REPORT, *supra* note 10, at 11.

operations overseas are that overseas testing is (1) more cost-effective and (2) easier to facilitate in terms of finding appropriate subjects.[33] The Tufts Center for the Study of Drug Development has estimated the cost of developing a new drug to be $1.3 billion,[34] which, in part, can be attributed to the costs of running clinical trials. The costs have risen because more new drugs are very similar to already approved drugs and, thus, sponsors need larger human subject pools to demonstrate the incremental advantages their experimental drug offers (although they do not have to demonstrate superiority for FDA approval standards).[35] It may also be less costly to find the necessary large number of subjects for Phase III trials overseas.[36] A *New England Journal of Medicine* report found that one third of the largest trials, Phase III trials, were conducted in foreign countries.[37] (The most crucial trial results for FDA purposes come from Phase III trials.[38]) In second- and third-world countries, subject recruitment is significantly less expensive; for example, in India, the cost per patient may be one tenth of what it is in the United States.[39]

Recruiting appropriate subjects is also easier overseas. Potential subjects in second- and third-world countries are less likely to be taking a drug already than their American counterparts.[40] Because medications potentially could complicate the study, "drug naïvety" is prized because it decreases the potential for "any unforeseen drug interactions, …" and the investigator does

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[33] *See* Yevgenia Shtilman, *Commentary, Pharmaceutical Drug Testing in the Former Soviet Union: Contract Research Organizations as Broker-Dealers in an Emerging Testing Ground for America's Big Pharma*, 29 B.C. THIRD WORLD L.J. 425, 428 (2009) (discussing the lower cost of conducting pharmaceutical testing overseas).

[34] *Drug Developers Are Aggressively Changing the Way They Do R&D*, TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT (Jan. 5, 2011), http://csdd.tufts.edu/news/complete_story/pr_outlook_2011.

[35] Roger Collier, *Rapidly Rising Clinical Trial Costs Worry Researchers*, 180 CANADIAN MED. ASS'N J. 277, 277 (2009).

[36] *Compare* Yasmine Chiu, Conducting Clinical Trials in Japan: A CRO Perspective, ppdi.com (Oct. 2013), at 3 (noting similar concerns in identifying sufficiently large clinical trial populations in Japan).

[37] Amanda Gardner, *Many Clinical Trials Moving Overseas*, U.S. NEWS AND WORLD REPORT(Feb. 18, 2009, 5:00 PM), http://health.usnews.com/health-news/managing-your-healthcare/research/articles/2009/02/18/many-clinical-trials-moving-overseas (explaining that the FDA typically looks at the results yielded from three phases of clinical testing); s*ee* U.S. FOOD & DRUG ADMIN., THE FDA'S DRUG REVIEW PROCESS: ENSURING DRUGS ARE SAFE AND EFFECTIVE, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (last updated Nov. 6, 2014). In Phase I, the trial is usually conducted with between 20 and 80 healthy human subject participants. *Id.* The FDA looks at "how the drug is metabolized and excreted" and its side effects. *Id.* In contrast, in Phase II, the FDA looks for a drug's effectiveness and approximately 24 to 300 human subjects with the condition or disease either receive the experimental drug or the placebo or another drug, and the results are compared. *Id.* In Phase III, between 200 and 3,000 human subjects are studied for additional information on the drug's effectiveness and safety, as well as for information on the drug's dosage and how it works when other drugs are combined with it. *Id.*

[38] 2010 HHS IG REPORT, *supra* note 10, at 3.

[39] *See* Gardner, *supra* note 37.

[40] Valerie Paris, *Why do Americans Spend so Much on Pharmaceuticals?*, PBS NEWSHOUR (Feb. 7, 2014), http://www.pbs.org/newshour/updates/americans-spend-much-pharmaceuticals/.

not have to exchange the patient's current medication for the drug on trial.[41] (Interestingly, however, in a study of CROs by the University of Pennsylvania's Dr. Adriana Petryna, sources voiced concern that data yielded from trials involving drug-naïve patients would not be generalizable to those "in treatment-saturated markets."[42])

Nevertheless, there are other, less publicized reasons for why a pharmaceutical sponsor may run its trial overseas. In addition to finding subjects more easily, there is often less stringent regulation overseas, allowing companies to run bigger trials in shorter periods of time. Moreover, other countries offer incentives to pharmaceutical sponsors to run trials using their population for economic reasons.[43] For example, the Russian government recently entered into an agreement with "an American venture capital firm," Domain Associates, to "jointly invest … $760 million in 20 biotechnology start-up companies in the United States."[44] The Russian government, which runs a national health system, is eager to improve its own biotech industry.[45] In return, Russia will "help these start-ups conduct 'advanced stage clinical trials in Russia of new pharmaceuticals."'[46]

Another lesser known reason for the shift to overseas trials is the ease with which companies can run placebo-controlled trials in overseas locations because the best standard of care may not always be available in poorer countries.[47] In the FDA's Guidance for Institutional Review Boards and Clinical Investigators, the FDA states that it does not have a preference that trials be placebo-controlled but, rather, that "the study design chosen must be adequate to the task."[48] Nevertheless, the FDA then goes on to say:

> It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early "escape" mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. … Placebo-controlled trials,

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[41] James Cekola, Comment, *Outsourcing Drug Investigations to India: A Comment on U.S., Indian, and International Regulation of Clinical Trials in Cross-Border Pharmaceutical Research*, 28 NW. J. INT'L L. & BUS. 125, 129 (2007).

[42] Petryna, *supra* note 31, at 37.

[43] *See* Talea Miller, *"Explosive" Growth in Foreign Drug Testing Raises Ethical Questions*, PBS NEWSHOUR (Aug. 23, 2011, 2:46 PM), http://www.pbs.org/newshour/rundown/sending-us-drug-research-overseas/. *See also* Shtilman, *supra* note 33, at 440.

[44] Andrew Kramer, *Guinea Pigs, for Their Health*, N.Y. TIMES (Sept. 26, 2012), http://query.nytimes.com/gst/fullpage.html?res=9E0DE2D81438F934A1575AC0A9649D8B63.

[45] *Id.*

[46] *Id.*

[47] Megan Landes, *Can Context Justify an Ethical Double Standard for Clinical Research in Developing Countries?*, 1 GLOBALIZATION & HEALTH 1, 2 (2005), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1183235/pdf/1744-8603-1-11.pdf.

[48] U.S. FOOD & DRUG ADMIN., DRUG STUDY DESIGNS—INFORMATION SHEET GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm (last updated Jan. 25, 2016).

> regardless of any advantages in interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.[49]

Furthermore, in 2000, when the Declaration of Helsinki was revised "to require the use of an active control unless none exists," the FDA refused to adopt the amendment.[50] In an active control trial, where the comparison is between the accepted drug and the new drug, attention must be paid to the "patient's compliance" and whether he or she takes "concomitant medications," both of which may affect the quality of the data negatively.[51] The Helsinki revision was adopted after placebos were used in African-based trials of a new protocol[52] of the AZT treatment that prevents "perinatal transmission of HIV."[53] Notably, these trials were funded in part by the United States Centers for Disease Control and Prevention and the National Institutes of Health, whose experts cited the regional culture and lack of health care as preventing the "best standard of care" from being given and local authorities' legal jurisdiction to determine what the best research protocols were.[54] In addition to the FDA's blessing of placebo-controlled trials, pharmaceutical sponsors are more likely to utilize them because they reduce costs.[55] Thus, the FDA's requirements and structural forces, such as the rising costs of trials, explain why current marketing applications for drugs contain so much foreign clinical trial data.

B. Contract Research Organizations Have Displaced Academic Institutions in Running Clinical Trials

CROs have displaced the traditional orchestrators of clinical trials: academic health centers (AHCs), which conduct drug research in an education setting.[56] CROs emerged as clinical trial research became more

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[49] *Id.*

[50] FOOD AND DRUG LAW, *supra* note 12, at 636.

[51] Petryna, *supra* note 31, at 30; s*ee also* ADRIANA PETRYNA, WHEN EXPERIMENTS TRAVEL 35-36 (Princeton University Press 2009).

[52] Laughton, *supra* note 20, at 188.

[53] Petryna, *supra* note 31, at 28.

[54] *Id.* at 29.

[55] *Id.* at 30.

[56] Philip Mirowski & Robert Van Horn, *The Contract Research Organization and the Commercialization of Scientific Research*, 35 SOC. STUD. OF SCI. 503, 506 (2005), note there are several academic contract research organizations. *See* Jeanne Lenzer, *Truly Independent Research?*, 337 BRIT. MED. J. 602, 602-6 (2008).

commercialized in the 1980s.[57] At roughly the same time, more trials began to be sent overseas, and the CRO industry experienced a boom. By the industry's own estimates, CROs grew rapidly during the last 30 years, from employing 12,000 people and enrolling 7 million subjects in 1992 to employing 94,000 people and enrolling 20 million subjects in 2001.[58]

Pharmaceutical sponsors prefer CROs to AHCs because of CROs' geographic flexibility, as well as their negotiating powers. CROs are able to recruit large numbers of patients because of their international presence, whereas AHCs are usually bound to the area in which their academic institution is located.[59] In addition, in terms of cutting costs, a multi-billion-dollar CRO likely has greater political and economic bargaining power in second- and third-world countries than its academic counterparts.[60] Moreover, countries with large human subject pools, like China and India, offer financial subsidies to CROs and Western pharmaceutical research and development initiatives.[61] For example, the state of Karnataka in India stated that it is "firmly committed to supporting" the work of contract research organizations citing that there is a "tremendous opportunity for Indian companies to do contract research for overseas corporations."[62] Finally, a CRO may be more willing to "engage in regulatory arbitrage."[63] Thus, the attractiveness of the CRO model is directly related to the increased overseas outsourcing of clinical trials. The CRO model also has supplanted pharmaceutical companies running their own clinical trials.[64] Today, CROs play a major role in running clinical trials abroad. According to a 2014 industry self-survey, CROs were active in the trials behind "85 of the 88 new drugs" approved by Europe and the United States in 2013.[65]

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[57] Mirowski & Van Horn, *supra* note 56, at 505. "Since the 1980s, pharmaceutical companies have increasingly outsourced clinical research." *See* WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 12.

[58] Mirowski & Van Horn, *supra* note 56, at 506.

[59] *Id.* at 516.

[60] *Id.* at 516. *See* Tim Sandler, *In India, Oversight Lacking in Outsourced Drug Trials*, NBC NEWS (Mar. 4, 2012, 5:31 PM), http://investigations.nbcnews.com/_news/2012/03/04/10562883-in-india-oversight-lacking-in-outsourced-drug-trials.

[61] Mirowski & Van Horn, *supra* note 56, at 517. "The Chinese government is encouraging foreign investment in R&D activities by granting tax incentives, providing financial subsidies and offering other incentives." *See* PricewaterhouseCoopers, *The Changing Dynamics of Pharma Outsourcing in Asia: Are You Readjusting Your Sights?*, INDUSTRIES PHARMACEUTICAL 23 (2008), *available at* http://www.pwc.be/en/pharma/the-changing-dynamics-of-pharma-outsourcing-in-Asia.pdf; 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, 669 (2013) (showing more evidence of China's and India's efforts to solicit foreign research and development initiatives).

[62] *See The Millennium Biotech Policy*, GOVT. OF KARNATAKA, p. 4 of http://www.nriforumkarnataka.org/policy/Bio%20Technology%20Policy.pdf (last visited Aug. 9, 2016).

[63] Mirowski & Van Horn, *supra* note 56, at 516.

[64] *Id.* at 513.

[65] Press Release, Association of Clinical Research Organizations (ACRO), *ACRO Survey Shows Strong Growth of CRO Industry* (Sept. 16, 2014), http://www.acrohealth.org/acro-survey-shows-strong-growth-cro-industry/.

II. IS THE FDA REVIEW PROCESS EQUIPPED TO HANDLE THE OUTSOURCING AND COMMERCIALIZATION OF CLINICAL TRIALS?

Overseas, commercially run trials are harder to regulate than their domestic counterparts, but the FDA review process is largely the same whether the trial is conducted overseas or domestically.[66] Section 314.106(b) of Title 21 of the Code of Federal Regulations states:

> An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.

The FDA's three steps for approving foreign clinical data are examined in depth below.

A. The FDA's Review Process and Foreign Clinical Trials

As mentioned earlier, clinical trials must show that the drug is both safe and effective by way of a "substantial evidence" standard.[67] The review process is managed by the FDA's Center for Drug Evaluation and Research (CDER), which examines the data yielded in clinical trials.[68] The process starts when an IND is submitted to the agency by the sponsoring pharmaceutical company.[69] The IND contains material on the trial's protocol and the experience of the trial staff, as well as documents testifying that the human subjects' wellbeing will be safeguarded.[70] The IND also exempts the sponsor from the federal law banning non-FDA-approved drugs from entering interstate commerce.[71] However, the FDA cannot always count on receiving an IND application when the trial is conducted abroad because submitting an

[66] 2010 HHS IG REPORT, *supra* note 10, at 6.
[67] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).
[68] Laughton, *supra* note 20, at 189-90.
[69] 2010 HHS IG REPORT, *supra* note 10, at 3.
[70] *See id.*
[71] Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(i)(2012); Public Health Service Act of 1944, 42 U.S.C. § 262(a)(2012).

IND is optional for companies conducting trials overseas.[72] Interstate commerce laws are not applicable abroad and, therefore, an IND is not required for a trial that is run completely outside the United States.[73]

As a result, the FDA's medical reviewers have noted that more and more sponsors are running trials abroad without INDs.[74] Under FDA regulations, an application based solely on foreign clinical data may be submitted, even if the trials were not done under an FDA IND, as long as "Good Clinical Practices"[75] were used in the trial.[76] The FDA requires that an Independent Ethics Committee (IEC) examine the study before it commences and that the IEC monitor the study as it advances and document human subjects' informed consent before the procedures begin.[77] The FDA also must have the opportunity to authenticate the trial data via an onsite inspection, if the FDA believes that it is needed.[78] Thus, the FDA's IND requirements are not as effective overseas as they are domestically.

Recently, the FDA has indicated that there may be differences in the efficacy results between foreign and domestic trials. In a July 2011 report, the FDA noted:

> Understanding variable characteristics in clinical trial sites is becoming increasingly important because of the international nature of current clinical trials. The sources of differences in efficacy results between U.S. and foreign clinical trial sites have yet to be determined, but differences rooted in the conduct of the clinical trial should be evaluated.[79]

However, the FDA continues to accept foreign clinical trial data, provided that the requirements are met.

B. The FDA's Review Process for Clinical Investigators and Contract Research Organizations

The FDA requires sponsors to choose qualified investigators and monitors to run and observe the studies (whether in the United States or abroad),

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[72] 2010 HHS IG REPORT, *supra* note 10, at 3.

[73] *See id.*

[74] 2010 HHS IG REPORT, *supra* note 10, at 17.

[75] 2010 HHS IG REPORT, *supra* note 10, at 3-4 (defining good clinical practices as "a 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 trial subjects are protected").

[76] 2010 HHS IG REPORT, *supra* note 10, at 3.

[77] U.S. FOOD & DRUG ADMIN., INFORMATION SHEET GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS FDA INSPECTIONS OF CLINICAL INVESTIGATORS 5-6 (June 2010), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf.

[78] COMPLIANCE PROGRAM GUIDANCE MANUAL, *supra* note 13, at 29.

[79] U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, IDENTIFYING CDER'S SCIENCE & RESEARCH NEEDS REPORT 23 (2011), http://www.fda.gov/downloads/Drugs/ScienceResearch/UCM264594.pdf.

"report adverse experiences," and maintain records.[80] In selecting monitors, the FDA requires sponsors to look at their training and experience in observing an investigational study,[81] and the same criteria apply to the sponsors' selection of clinical investigators.[82] The FDA also has an interest in how clinical investigators, including those overseas, are paid by the sponsors due to concerns about bias.[83] Regulations require applicants to disclose certain contracts between the sponsor and the clinical investigator.[84] The FDA considers a payment from a sponsor to a clinical investigator to be "significant" if it is more than $25,000, not considering the actual costs of the clinical study.[85] Such disclosures play a part in the FDA's evaluation of the data's reliability.[86] When the FDA believes that the integrity of the data has been compromised due to the financial interests of the investigator, the FDA may initiate an audit of the questionable data, ask for additional data, request an independent study, or reject the study altogether.[87]

The FDA has the option of inspecting clinical investigators overseas if the study is relevant to the marketing application that has been received by the FDA and contains critical data.[88] This applies to international studies that are conducted under an IND and international studies that are not run under an IND.[89] The FDA also may investigate how sponsors interact with investigators when there is a severe deviation from FDA regulations or the investigational plan and the FDA then may investigate how the sponsor subsequently obtained compliance.[90] Finally, the FDA may investigate if noncompliant investigators were not terminated properly.[91]

The FDA's inspection authority also applies to a CRO if the sponsor has contracted with the CRO to run the trial (i.e., evaluate reports, select

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[80] U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS, at Part I, 1 (Mar. 11, 2011), http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133770.pdf.

[81] *Id.* at Part III, 5-6.

[82] *Id.*

[83] 21 C.F.R. § 54.1 (2014).

[84] 21 C.F.R. § 54.4 (2014).

[85] 21 C.F.R. § 54.2 (2014); s*ee also* Wilson, *supra* note 61, at 679-80(arguing that the FDA should consider revising this number in light of the fact that, "while $ 25,000 is a relatively nominal sum for an American doctor, the same amount might represent more than the annual salary of a doctor in a less prosperous country and significantly more than a year's wages in a developing country").

[86] 21 C.F.R. § 54.1 (2014).

[87] 21 C.F.R. § 54.5 (2014).

[88] FDA INSPECTIONS OF CLINICAL INVESTIGATORS, INFORMATION SHEET GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS *supra* note 77, at 5.

[89] *Id.*

[90] U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS, *supra* note 80, at Part III, 6.

[91] *Id.*

study monitors and investigators, or work on protocol design).[92] Many sponsors also allow CROs to determine where the investigation will take place and have moved investigative site management to CROs.[93] Additionally, CROs are often responsible for updating the informed consent form as adverse events materialize.[94] However, the FDA has few guidance documents on the relationship between a CRO and a sponsor, despite CROs' increased role in running clinical trials.

FDA guidance documents and federal regulations allow for the transfer of authority from a sponsor to a CRO. According to an FDA guidance document, once a contract exists between a pharmaceutical sponsor and a CRO, "responsibility as well as authority may be transferred and thus the CRO becomes a regulated entity."[95] In order for a transfer of responsibilities to occur, there must be a written agreement[96] that is submitted to the FDA.[97] The FDA states that a CRO that takes on a sponsor's obligations must follow the appropriate FDA regulations regarding the sponsor's obligations and that the CRO will "be subject to the same regulatory action as a sponsor" if it does not comply with the aforementioned obligations.[98] The FDA also has put forth nonbinding guidance stating, "Although sponsors can transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the work completed by the CRO(s) that assume this responsibility."[99] Furthermore, the FDA has set forth that a sponsor should oversee a CRO's "compliance with regulatory requirements and contractual obligations in an ongoing manner."[100] According to the FDA, such oversight may consist of the sponsor conducting a "periodic review" of the CRO's monitoring of the trial.[101] Thus, although the FDA allows a sponsor to transfer authority for a human subjects clinical

[92] *Id.* at 4; *see also* WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 25 (stating that, "[m]ost CROs are involved in locating research sites, recruiting patients, and, in some cases, drawing up the study design and performing analyses. … Some even have their own centralized institutional review boards.").

[93] Sonia Valdes & Penny McGuire, *Contract Research Organizations (CROs) May Be the Next Trend in Clinical Trials Liability*, 7 J. BIOLAW & BUS. 11, 12 (2004).

[94] *Id.* at 14.

[95] COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS, *supra* note 80, at Part II, 1.

[96] *Id.* at Part I, 2.

[97] *Id.* at Part III, 3.

[98] 21 C.F.R. § 312.52 (2014).

[99] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY OVERSIGHT OF CLINICAL INVESTIGATIONS—A RISK-BASED APPROACH TO MONITORING 18 (Aug. 2013), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

[100] *Id.*

[101] *Id.*; *see also Accountability for CROs is Weak*, ACCESS TO MEDICINE FOUNDATION, http://2012.atmindex.org/accountability-cros-weak (last visited Apr. 10, 2016) (stating "Only four companies provide evidence that they use disciplinary measures to enforce codes of conduct in relation to the Contract Research Organisations (CROs) they employ to conduct clinical trials on their behalf in developing countries").

trial to an outside party, it is questionable how much oversight it actually requires.

Furthermore, the FDA does not appear to have guidance documents on how liability must be apportioned in a contract between a CRO and a sponsor. The FDA only advises that "[s]ponsors and CROs should prospectively establish a clear understanding of both parties' responsibilities and of the expectations for the conduct of the transferred obligations."[102] In their contracts with sponsors, insurance companies advise CROs to have the sponsor assume any liability for human subjects' care.[103] However, they also acknowledge that, given the competitive CRO marketplace, CROs often lose out on the safeguards that warranties and indemnity provisions provide, in exchange for a contract.[104] There are very few litigated cases on record regarding disputes between a sponsor and a CRO. This may be the result of arbitration clauses in the contracts between CROs and sponsors.[105]

Overall, there are also few court cases on record regarding American CROs' international operations. Although there has been an increase in clinical trial litigation domestically, [106] CROs acting overseas generally have not been subject to public legal action from human subject participants or, more important, the United States government. For example, in the United States, human subject participants have sued CROs, claiming that they were not given access to proper medical care.[107]

In addition, a CRO's contractual relationship with the sponsor may create conflicts of interest not addressed by the FDA's current guidance documents. CROs may elect not to report sponsors' violations to the FDA out of fear of harming future business prospects.[108] As recently as 2007, Rachel Behrman, director of the FDA's Office of Critical Path Programs, told the *New England Journal of Medicine*, "[I]t's not clear whether [the CRO's] accountability is through the sponsor or directly to us."[109] Dr. Petryna cites CROs' concerns that they are often not in a position to refuse a sponsor's risky protocols or to report adverse effects, knowing that, if they do, the trial and the company's contract

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[102] *Oversight of Clinical Investigations, supra* note 99, at 18 (advising that "[s]ponsors should share information with a CRO that may inform decisions a CRO may make regarding the monitoring practices for a trial …").

[103] Valdes & McGuire, *supra* note 93, at 14.

[104] *Id.*

[105] *See* Zila Biotechnology, Inc. v. Quintiles, Inc., No. CV 08-2139, 2009 U.S. Dist. LEXIS 47463, at **1-2 (D. Ariz. May 21, 2009). Zila hired Quintiles to run a drug study and later accused Quintiles of ruining the study. However, the case involved not the ruined study but rather whether the terms of the "agreed-upon provisions pertaining to dispute resolution" could be modified by the future arbitrator.

[106] Michelle M. Mello et al., *The Rise of Litigation in Human Subjects Research*, 139 ANNALS INTERNAL MED. 40, 40 (2003).

[107] Valdes & McGuire, *supra* note 93, at 14 (citing the CenterWatch study).

[108] *Id.*

[109] Miriam Shuchman, *Commercializing Clinical Trials—Risks and Benefits of the CRO Boom*, 357 NEW ENG. J. MED. 1365, 1365-66 (2007) (internal quotation marks omitted).

may be halted.[110] As stated earlier, contractual disputes between sponsors and CROs may be resolved with arbitration provisions, and there are few litigated cases on record.

Disturbingly, Dr. Petryna also found that, if a CRO rejects a sponsor's "risky protocol" bid, the sponsor will simply find a new CRO that will accept it.[111] Quintiles, one of the largest CROs, has been criticized for running ads targeted at pharmaceutical sponsors with the slogan, "The answer is yes," with critics arguing that CROs should exercise more discretion.[112] The FDA does not publicly disclose which CROs' sponsors use or whether a sponsor switches CROs.

The FDA is also not able to keep track of all trials run by CROs. CROs are increasingly under pressure from sponsors to cut costs, because the cost for clinical trials is becoming the most expensive aspect of research and development.[113] Efficiency is prized, and poorly performing trials may be terminated early by the CRO on behalf of the sponsor.[114] If the trial is not performed under an IND, the FDA is unaware if a trial is terminated early.[115]

Finally, although the FDA has detailed guidance documents on how clinical trials must be conducted, guidance regarding the sponsor's contract with a CRO on how a clinical trial should be run is lacking. Executives of CROs and sponsors have both expressed concern about the scarcity of FDA guidelines recently.[116] As CROs cut costs to stay competitive, pressure on the investigators increases.[117] Surveys have shown that investigators give lower marks to sites run by CROs than to sites run by sponsors.[118] There is high turnover among CRO employees, especially those based outside the United States.[119] CRO executives have tied poor site performance to fraud and human subjects protection violations.[120] Of note, although CROs are often under

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[110] WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 81-82.

[111] *Id.* at 26, 105.

[112] Matthew Herper, *Money, Math and Medicine*, FORBES (Nov. 3, 2010, 6:00 PM), http://www.forbes.com/forbes/2010/1122/private-companies-10-quintiles-dennis-gillings-money-medicine_2.html.

[113] Valdes & McGuire, *supra* note 93, at 11.

[114] Mirowski & Van Horn, *supra* note 56, at 534 (pointing out that early termination has adverse effects for the patients involved in the trial, violating the Helsinki Declaration). Furthermore, future human subjects may be subject to duplicative research by another company for the failed drug as sponsors typically do not release data on failed trials. *Id.*

[115] 2010 HHS IG REPORT, *supra* note 10, at ii.

[116] Zachary Brennan, *Executives Raise Questions on Clinical Trial Sponsors' Oversight of CROs*, OUTSOURCING-PHARMA.COM (May 13, 2013), http://www.outsourcing-pharma.com/Product-Categories/Phase-I-II/Executives-Raise-Questions-on-Clinical-Trial-Sponsors-Oversight-of-CROs.

[117] Valdes & McGuire, *supra* note 93, at 12.

[118] *Id.* (citing the CenterWatch survey).

[119] Zachary Brennan, *Survey: CROs See Rise in Employee Turnover Rate, Less Retention Bonuses*, OUTSOURCING-PHARMA.COM (Mar. 27, 2013), http://www.outsourcing-pharma.com/Commercial-Services/Survey-CROs-See-Rise-in-Employee-Turnover-Rate-Less-Retention-Bonuses.

[120] Valdes & McGuire, *supra* note 93, at 12 (citing the CenterWatch survey).

pressure from sponsors to cut costs, the arena remains a billion-dollar industry. In 2016, CRO revenue was "expected to reach $27.8 billion."[121]

C. The FDA Rarely Inspects Foreign Clinical Trial Sites

The FDA has stated that "[a]lthough [it] has the authority to conduct site inspections, it is not required to do so."[122] The FDA may pursue an international inspection if the clinical trial is for an FDA marketing application and is the source of key data that the FDA will examine when deciding whether to approve the product or not.[123] Furthermore, inspections may be assigned even if the study is not performed under an IND.[124] The FDA, however, may not be aware of a trial if an IND has not been submitted.[125]

The FDA's Office of Scientific Investigations runs BIMO and works with medical reviewers on which clinical trials to examine.[126] The Office of Scientific Investigations collaborates with the Office of Regulatory Affairs, which conducts the majority of inspections.[127] BIMO has stated that its mission is to protect the rights of research subjects and ensure the integrity of the clinical trial data it receives.[128] Inspectors review the procedures and practices of the sponsors, the CROs, and the monitors to evaluate their compliance with FDA regulations.[129] Inspections involve comparing the clinical investigators' source documents and "case report forms" with the clinical trial data the FDA has received from the sponsor.[130] For example, one key item that investigators look to verify is "if the number of subjects in the studies performed under an IND is the same as the number reported in the NDA" (i.e., New Drug

[121] *Fact Sheet*, ASS'N OF CLINICAL RES. ORG., http://www.acrohealth.org/media-center/fact-sheet/ (last visited Aug. 7, 2016).
[122] 2010 HHS IG Report, *supra* note 10, at 4.
[123] COMPLIANCE PROGRAM GUIDANCE MANUAL, *supra* note 13, at 4.
[124] *Id.* at 4.
[125] 2010 HHS IG REPORT, *supra* note 10, at ii.
[126] *Id.* at 4; *see also* U.S. FOOD & DRUG ADMIN., OFFICE OF SCIENTIFIC INVESTIGATIONS METRICS 2 (Jan. 2013), http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM256376.pdf (providing more information about the inspections).
[127] CONSTANCE LEWIN, U.S. FOOD & DRUG ADMIN., CDER'S ROLE IN FDA'S BIORESEARCH MONITORING PROGRAM AND HUMAN SUBJECT PROTECTION 8, *available at* http://www.fda.gov/downloads/Drugs/NewsEvents/UCM182563.pdf; *see also* U.S. FOOD & DRUG ADMIN., OFFICE OF SCIENTIFIC INVESTIGATIONS, METRICS 2 (Jan. 2014), http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM256376.pdf.
[128] U.S. FOOD & DRUG ADMIN., BIORESEARCH MONITORING PROGRAM (BIMO), http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm (last visited Apr. 11, 2016).
[129] U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS, *supra* note 80, at Part III, 1.
[130] COMPLIANCE PROGRAM GUIDANCE MANUAL, *supra* note 13, at Part III, 11.

Application).[131] The FDA's BIMO staff also ensures that adverse events are adequately documented.[132]

Disturbingly, in its guidance to the BIMO staff, the FDA has stated that "[i]f it is a 'for cause' or surveillance inspection of an on-going study, data comparison will generally involve only source documents and case report forms, because there may not always be data supplied by the sponsor."[133] The OIG cited FDA staff testimonials that "application files were missing," and sponsors did not always disclose in their reports total subject enrollment and the location of sites.[134] As a result, the FDA's ability to protect human subjects and ensure data integrity is severely hampered by missing data.

Inspections can sometimes unearth serious flaws in a trial. For instance, in a 2005–2009 BIMO investigation of an IND application from Pfizer, Inc., Pfizer was cited for failing "to ensure proper monitoring of the investigation," and, "as a result of inadequate monitoring, widespread overdosing of study subjects at multiple study sites was neither detected nor corrected in a timely manner."[135] The FDA noted that one of the pediatric subjects "experienced 12 days of overdosing with moderate akathisia and severe tremor."[136] The FDA also cited Pfizer for failing to guarantee that the study was conducted in line with the IND application's protocols.[137] Pfizer's noncompliance with FDA regulations regarding pediatric trials is notable given the infamous case of its pediatric testing of Trovan in Nigeria.[138]

In 1996, Pfizer tested trovafloxacin (i.e., Trovan) on 100 Nigerian children suffering from meningitis during an emergency outbreak.[139] Eleven children died and others were left severely disabled.[140] In subsequent lawsuits, the families claimed that Pfizer did not disclose that Trovan was an experimental drug and that their children could have received the established treatment for free from Médecins Sans Frontières (i.e., Doctors Without Borders), which was operating in the same hospital as Pfizer.[141] The case is also notable for

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[131] U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS, *supra* note 80, at Part III, 10.

[132] COMPLIANCE PROGRAM GUIDANCE MANUAL, *supra* note 13, at Part III, 9.

[133] *Id*. at Part III, 1 (explaining that "[s]ource documents may include office records, hospital records, laboratory reports, records of consultations, etc").

[134] 2010 HHS IG REPORT, *supra* note 10, at ii.

[135] LESLIE BALL, U.S. FOOD & DRUG ADMIN., INSPECTIONS, COMPLIANCE, ENFORCEMENT, AND CRIMINAL INVESTIGATIONS, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm208976.htm#.T2S7IFKwpA4.email (last updated Mar. 23, 2016).

[136] *Id.*

[137] *Id.*

[138] *See* 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.

[139] Jeanne Lenzer, *Nigeria Files Criminal Charges against Pfizer*, 334 BRIT. MED. J. 1181, 1181 (2007).

[140] *Id.*

[141] *Id.*

the jurisdiction questions it created; in June 2010, the Supreme Court denied Pfizer's petition for a writ of certiorari, allowing the Nigerian's claims to proceed to trial.[142] In its brief to the Supreme Court, Pfizer argued that the Second Circuit's expansion of the Alien Tort Statute's (ATS) jurisdiction to allow the Nigerians' complaints to go forward was contrary to precedent.[143] Specifically, Pfizer argued that the Nigerians' allegations that there was no informed consent requested by Pfizer, a private actor, should not be considered "an international law violation enforceable in a U.S. court under the ATS."[144] Pfizer ultimately settled the case for $35 million.[145] The negative publicity generated from the Trovan trial and the subsequent settlement may be one reason why Pfizer now outsources some of its clinical trials to CROs.[146] Pfizer's own researchers conducted the Trovan trial.[147] Pfizer's previous history also may account for why the FDA chose to inspect the company's 2005 pediatric study.

Typically, however, the main factors that the FDA takes into consideration when prioritizing where and whom to inspect are whether there is a sizeable number of enrolled subjects and "whether the site had a large effect on efficacy results, had data inconsistencies, had statistical outliers, or was part of an original application."[148] For international inspections of sponsors, the FDA focuses on sponsors that are based outside the United States and what the conduct of the study is likely to be.[149] As will be discussed later in this article, the FDA is planning to utilize a "site selection tool" that will prioritize inspection sites "based on risk factors unique to a particular clinical trial."[150] Although the FDA has the option of inspecting clinical trials in "real time," the majority of inspections are not completed until after the marketing application is submitted to the FDA, and then the FDA primarily focuses on validating the accuracy of the clinical data.[151] When the FDA's clinical trial

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[142] Abdullahi v. Pfizer, Inc., 562 F.3d 163, 172 (2d Cir 2009), Pfizer, Inc. v. Abdullahi, 561 U.S. 1041 (2010), *cert. denied.*

[143] Petition for Writ of Certiorari, Pfizer, Inc. v. Rabi Abdullahi, et al., 561 U.S. 1041 (2009) (No. 09-34).

[144] *See id.* See Brady Bizarro, *"Vigilant Doorkeeping": Post-Kiobel Corporate Accountability under the Alien Tort Statute for Negligence and Violations of the International Prohibition on Nonconsensual Medical Experimentation*, 33 B.U. INT'L L.J. 137-83 (2015) for a discussion of how the 2013 *Kiobel* case (Kiobel v. Royal Dutch Petroleum Co., 133 S. Ct. 1659 (2013)) affects the ability of trial participants to bring a case under the ATS.

[145] Donald McNeil Jr., *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.

[146] Andrew McConaghie, *Pfizer Simplifies Contract Research with Parexel and Icon*, PHARMAFILE (May 27, 2011), http://www.pharmafile.com/news/157913/pfizer-simplifies-contract-research-parexel-and-icon (stating currently Pfizer contracts with several CROs, including Parexel).

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

[148] 2010 HHS IG REPORT, *supra* note 10, at 16.

[149] INFORMATION SHEET GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS FDA INSPECTIONS OF CLINICAL INVESTIGATORS, *supra* note 77, at 5.

[150] 2010 HHS IG REPORT, *supra* note 10, at 18.

[151] *Id.* at 3-4.

regulatory process is based almost entirely on a review of clinical trial records after the trial was conducted rather than real-time inspections, the FDA is unable to halt or remedy a trial that lacks good clinical practices.

Even when the FDA is able to conduct a real-time inspection, notice requirements and jurisdiction questions hamper its effectiveness. The FDA generally pre-announces its inspections, although the field investigator is instructed to minimize the time between the announcement and the actual inspection and to report if the sponsor (or its CRO) tries to "unduly delay … an inspection, by more than ten working days."[152] If the sponsor refuses an inspection, FDA personnel are instructed to remind the sponsor of the FDA's legal authority under the FDCA and the Public Health Service Act.[153] If the sponsor or its CRO prevents the FDA from accessing records to which it is entitled, the FDA's field investigator is to inform the appropriate company about the FDA's legal authority.[154] Nevertheless, whether the laws in question have extraterritorial application is a matter of debate, as addressed later in this article.

Finally, the FDA is often barred from inspecting a trial in the first place due to cost concerns. For instance, in 2010, the HHS OIG recommended a closer examination of Phase I trials "because they may pose more risks for subjects," but the FDA responded that it was limited by "resource constraints."[155] The average inspection costs approximately $40,000.[156]

Resource constraints do not just affect the FDA's ability to inspect overseas Phase I trials. In the same 2010 HHS OIG report, analysts found that the FDA inspected a mere "0.7 percent of foreign clinical trial sites" in 2008.[157] In fiscal year 2014, CDER completed just 214 international inspections.[158] The low rate of international inspections should be considered alongside the fact that from 1998 to 2008, the number of clinical investigators running trials overseas pursuant to an IND "more than doubled,"[159] and the majority of clinical trial sites are now located in foreign countries.[160] In addition to this severe lack of oversight, the federal government is hampered by its inability to take adequate enforcement actions.

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[152] INFORMATION SHEET GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS FDA INSPECTIONS OF CLINICAL INVESTIGATORS, *supra* note 77, at 12.

[153] *Id.*

[154] *Id.*

[155] 2010 HHS IG REPORT, *supra* note 10, at 39.

[156] *Id.* at 18.

[157] *Id.* at ii.

[158] U.S. FOOD & DRUG ADMIN., *Bioresearch Monitoring (BIMO) Metrics—FY'14*, 13 (April 2015), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM443775.pdf.

[159] 2010 HHS IG REPORT, *supra* note 10, at 13.

[160] Glickman et al., *supra* note 29, at 816.

III. IS THE FEDERAL GOVERNMENT ABLE TO TAKE APPROPRIATE ENFORCEMENT ACTIONS?

Enforcement actions against CROs are addressed first because they are now the primary orchestrators of overseas clinical trials. In particular, this part focuses on the Foreign Corrupt Practices Act (FCPA) and whether the Department of Justice (DOJ) can use this law to target corruption in overseas clinical trials run by CROs. This part then examines the FDA's standard enforcement actions and how the outsourcing of clinical trials has hampered the agency's ability to prevent regulatory violations.

As CROs are asked to take on potentially risky trials, there is the question of how much legal liability the CROs absorb. As stated earlier, under FDA regulations, sponsors may transfer some responsibilities to CROs, and CROs may be subject to FDA actions. This transfer of responsibility should be kept in mind as CROs handle local regulatory bodies for sponsors, which potentially may give rise to actions forbidden under the FCPA.

CROs often advertise themselves as specializing in the legal and regulatory environments of foreign countries.[161] Pharmaceutical sponsors often do not have experience with regional regulators, which is, in part, why they rely on CROs to facilitate international clinical trials.[162] CROs highlight their knowledge of local government structures and foreign customs to sponsors.[163] In the majority of foreign countries, the government, not the private sector, runs medical services.[164] CROs sometimes advertise that the foreign countries in which they operate have less rigorous clinical trial approval procedures. Quintiles, one of the largest CROs, notes that there is an "uncomplicated regulatory approval process" in South Africa.[165] At the same time, CROs promise to cut costs and shorten the overall trial process.[166]

With the increase in CRO-run trials overseas, problems have emerged. Recently in India, concerns were expressed about CROs operating on behalf of

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[161] Petryna, *supra* note 31, at 26. "[CROs] organize and monitor all stages of global multi[-]sited trials and guide clients through complex national regulatory environments." WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 4, 16.

[162] Mirowski & Van Horn, *supra* note 56, at 511.

[163] *See International Full-Service Contract Research Organization*, JANIX 4 (2012), http://www.janix.com/janix_brochure_2012.pdf. CROs also may use subcontractors to make these connections. Dr. Petryna investigated a CRO using an American-founded subcontractor operating in Poland that "advertises itself as knowing local customs and having connections to drug regulatory agencies." WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 106. "In this frontier, responsibility for the conduct of the trial and for insurance, along with civil liability, is continuously transferred to third parties who would in practice prove difficult to track." *Id.* at 107.

[164] Drew A. Harker & Chad E. Miller, *The Foreign Corrupt Practices Act and Clinical Trials: A Trap for the Unwary*, 63 FOOD DRUG L.J. 509, 515 (2008).

[165] *See Fact Sheet Phase II/III Global Clinical Development: Access Vast Patient Populations and Clinical Resources: Sub-Saharan Africa*, QUINTILES 1-2 (2010), http://www.quintiles.com/~/media/library/fact%20sheets/subsaharan-africa-access-vast-patient-populations.pdf.

[166] Petryna, *supra* note 31, at 25; *see also* WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 16.

foreign pharmaceutical sponsors; specifically, Indian medical journal experts have warned that the Indian government poorly regulates the CRO industry.[167] An American television program, *Dateline*, posed as a fictitious American drug sponsor and was able to enter into negotiations with two of India's main CROs, Lambda Therapeutic Research and Synchron Research Services, to test a drug that was equivalent to Vioxx, which has been internationally discredited and tied to thousands of deaths.[168] Lambda consented to run the trial even after noting to the fictitious sponsor that the drug was no longer on the international market.[169] Synchron claimed that it would never run such a trial only after it was revealed that the sponsor was fictitious.[170] Synchron has American ties.[171] In 2008, American-based CRO Parexel announced it was expanding its minority interest ownership in Synchron's Phase I business to 31%.[172] Although there is no evidence of bribery in the example above, other American CROs operating overseas may be subject to United States enforcement actions if the DOJ can find evidence of certain types of corruption.

One potential tool the United States government has to root out corruption in overseas foreign clinical trials is the FCPA. The FCPA was enacted to deter "bribery of foreign officials" and its provisions make it illegal for Americans to corruptly pay foreign authorities "in order to assist … in obtaining or retaining business for or with, or directing business to, any person."[173] In a 2009 address to a pharmaceutical industry forum, Lanny A. Breuer, assistant attorney general for the DOJ's Criminal Division, indicated that the DOJ would use the FCPA to target corruption in overseas pharmaceutical arenas.[174]

> Consider the possible range of "foreign officials" who are covered by the FCPA: Some are obvious, like health ministry and customs officials of other countries. But some others may not be, such as the doctors, pharmacists, lab technicians and other

[167] Sandler, *supra* note 60. In 2013, the Indian government moved to revamp its regulatory system after seven people died in human papillomavirus (HPV) vaccine clinical trials. *See* Zachary Brennan, *Indian Clinical Trial Reforms Take Shape as Report Condemns HPV Vaccine Trials*, OUTSOURCING-PHARMA.COM (Sept. 10, 2013, 2:06 PM), *available at* http://www.outsourcing-pharma.com/Clinical-Development/Indian-Clinical-Trial-Reforms-Take-Shape-as-Report-Condemns-HPV-Vaccine-Trials. The American lobby for CROs, ACRO, was actively involved and persuaded the Indian government to scale back proposals on the compensation to be provided to patients who did not see a therapeutic benefit from a trial. *Id.*

[168] Sandler, *supra* note 60.

[169] *Id.*

[170] *Id.*

[171] *Press Release: PAREXEL International Expands Relationship with Synchron Research in India and Divests Bioanalytical Laboratory in France*, PAREXEL (Mar. 27, 2008), http://investor.parexel.com/phoenix.zhtml?c=94569&p=irol-newsArticle&ID=1122623&highlight.

[172] *Id.*

[173] U.S. DEP'T OF JUSTICE AND SECURITIES & EXCHANGE COMM'N, A RESOURCE GUIDE TO THE U.S. FOREIGN CORRUPT PRACTICES ACT 2, JUSTICE.GOV (Nov. 14, 2012), http://www.justice.gov/criminal/fraud/fcpa/guide.pdf (citing 15 U.S.C. §§ 78dd-1(a)-78dd-3(a) (1998)).

[174] *See* 15 U.S.C. § 78 (1998).

> health professionals who are employed by state-owned facilities. … The depth of government involvement in foreign health systems, combined with fierce industry competition and the closed nature of many public formularies, creates a significant risk that corrupt payments will infect the process.[175]

Prominent law firms construed this as possibly including foreign medical researchers.[176] Earlier in 2008, white-collar criminal defense lawyers began advising sponsors working with CROs in corrupt countries to have their paperwork in order to avoid being held liable for any potential mishaps.[177] If this is the case, the "process" to which Assistant Attorney General Breuer referred may include the clinical trials mentioned above, with which the FDA is concerned.

Based on a review of the DOJ's website, it currently appears that the department only has taken one public action under the FCPA regarding the conduct of clinical trials. However, according to HHS reports, the potential for improprieties exists.[178] Given CROs' advertising pitches to sponsors about their ability to navigate local regulatory structures and customs, there is, presumably, some relationship between CROs and foreign governments. Industry watchers have suggested that the FCPA is a potential avenue the federal government could use to target improprieties in the CRO market.[179]

At a 2011 FCPA compliance event for CROs and other life sciences companies, "high risk enforcement area" discussions included "[f]oreign clinical trials due diligence and monitoring, particularly within emerging markets."[180] It was also noted that the DOJ and the Securities and Exchange Commission (SEC) had begun investigating "payments made overseas" to, among other things, "influence drug trials."[181] Furthermore, several large pharmaceutical companies, such as Bristol-Myers Squibb, Merck, GlaxoSmithKline, and AstraZeneca, revealed that they were under investigation "for possible

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[175] *See* Mike Koehler, *A Few Questions from the Back Row*, FCPA PROFESSOR (Nov. 12, 2009), http*://fcpaprofessor.blogspot.com/2009/11/few-questions-from-back-row.html*(referring to LANNY A. BREUER, PREPARED KEYNOTE ADDRESS TO THE TENTH ANNUAL PHARMACEUTICAL REGULATORY AND COMPLIANCE CONGRESS AND BEST PRACTICES FORUM, 2, JUSTICE.GOV (Nov. 12, 2009).

[176] *See Heightened Scrutiny of Foreign Clinical Trials*, ARNOLD & PORTER LLP 1 (July 2010), http://files.arnoldporter.com/advisory-heightened_scrutiny_of_foreign_clinical_trials_071210.pdf.

[177] Harker & Miller, *supra* note 164, at 520 ("Reducing all understandings to writing, especially those regarding the FCPA is essential, particularly in those countries with a history of corruption.").

[178] U.S. DEP'T OF HEALTH & HUMAN SERV., OFFICE OF THE INSPECTOR GEN., THE GLOBALIZATION OF CLINICAL TRIALS: A GROWING CHALLENGE IN PROTECTING HUMAN SUBJECTS, ii (Sept. 2001), http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf (hereinafter 2001 HHS IG REPORT).

[179] *See* Wilson, *supra* note 61, at 681-85 (discussing in detail how the DOJ could use the FCPA to target fraud in the CRO industry).

[180] *5th National Conference on the FCPA and Anti-Corruption for the Life Sciences Industry, The Preeminent FCPA Compliance Event for CROs, Pharmaceutical, Medical Device and Biotechnology Companies*, AM. CONFERENCE INST., http://www.americanconference.com/2011/751/fcpa-and-anti-corruption-for-the-life-sciences-industry (last visited Apr. 10, 2016).

[181] *Id.*

violations of the Foreign Corrupt Practices Act," and sources told the *Wall Street Journal* that "[s]ome of the alleged bribes could involve payments to doctors to influence drug trials."[182]

Nonetheless, any potential DOJ investigations may have been hampered by recent private buy-outs of CROs. The FCPA applies to both issuers, which are companies "with a class of securities listed on a national securities exchange in the United States, or any company with a class of securities quoted in the over-the-counter market in the United States and required to file periodic reports with SEC," and domestic concerns, which include "any corporation, partnership, association, joint-stock company, business trust, unincorporated organization, or sole proprietorship that is organized under the laws of the United States … that has its principal place of business in the United States."[183] CROs in the United States, many of which are situated in the Northeast,[184] are covered by the FCPA as domestic concerns. However, in the past few years, many prominent, publicly traded CROs have gone private and, thus, can no longer be considered "issuers" for the purposes of the FCPA. This is a reversal from the 1990s when "many CROs went public."[185]

In 2002, the Sarbanes-Oxley Act (SOX) was signed into law.[186] Data yielded from SOX disclosures are a key component of FCPA actions.[187] In 2003, Quintiles was the first CRO to be taken private (by senior management).[188] In 2009, when Assistant Attorney General Breuer announced the DOJ's plans to target corruption in overseas pharmaceutical arenas, Averion and PharmaNet were taken private, with four more CROs following suit in 2010–2011, including PPD, Kendle, Theorem Clinical, and InVentiv Clinical.[189]

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[182] Ashby Jones, *Feds Introducing BigPharma to FCPA*, WALL ST. J. L. BLOG (Oct. 5, 2010, 8:58 AM), http://blogs.wsj.com/law/2010/10/05/feds-introducing-bigpharma-to-fcpa/.

[183] U.S. DEP'T OF JUSTICE et al., *supra* note 173, at 11.

[184] Petryna, *supra* note 31, at 23.

[185] *Id.* at 26.

[186] *See* THE LAWS THAT GOVERN THE SECURITIES INDUSTRY, SECURITIES AND EXCHANGE COMM'N, http://www.sec.gov/about/laws.shtml#sox2002 (last visited Apr. 11, 2016).

[187] Michael Volkov, *The Relationship between Sarbanes-Oxley and FCPA Compliance*, THE VOLKOV LAW GROUP, LLC (Jan. 15, 2014), http://corruptioncrimecompliance.com/2014/01/the-relationship-between-sarbanes-oxley-and-fcpa-compliance/. "In many respects, the voluntary disclosure process which has fueled the FCPA enforcement program is the result of reforms required by Sarbanes-Oxley. Prior to Sarbanes-Oxley, companies may not have been required to disclose an FCPA violation to the public, which in turn would permit the company to resolve the matter internally without having to report the violation to the Justice Department and the SEC." *Id.*

[188] Jim Miller, *Contract Services in 2012, Some Recent Private-Equity Buyouts of CROs Show Both the Upside and Downside for Investors*, 25 BIOPHARM INT'L 18, 19 (2012).

[189] *See generally* Miller, *supra* note 188. In August 2015, Chiltern (a privately held CRO) acquired Theorem Clinical. *Chiltern Announces Agreement to Acquire Theorem Clinical Research*, CHILTERN (Aug. 6, 2015), http://www.chiltern.com/about-us/news/chiltern-announces-agreement-to-acquire-theorem-clinical-research/.

As of September 2015, Quintiles, PRA International, Averion,[190] and Kendle (now part of INC) had gone public again, with at least two citing financial difficulties as the reason for their return to the United States stock market.[191] After seven years of being exclusively owned by private equity, in 2014 PRA International (now PRA Health Sciences) allowed "public shareholders to own about 30 percent of the company, after the IPO," using the proceeds to pay down PRA's $1.3 billion debt load.[192] Thus, CROs that have chosen to go private have not always fared well financially.

However, as several industry watchers have noted, going private may allow a company to hide noncompliant behavior. For example, after the CRO PPD went private, commentators noted that it would be able to shield its operations from intrusive questioning by public investors, similar to what PharmaNet Development was able to do after a private-equity firm bought it shortly after it emerged there were issues of "noncompliant behavior" in its management of clinical trials.[193] In addition, "'By becoming a private company, PPD will face significantly less regulatory scrutiny,' said University of North Carolina Wilmington professor Ed Graham."[194]

The DOJ has stated, "The [FCPA's] accounting provisions do not apply to private companies."[195] For example, if a CRO were publicly held and were an "issuer," it would be required to keep accurate accounts and books that listed transactions in detail so that the government could determine whether a

[190] Averion merged with several other CROs in 2010 to become the privately held Aptiv Solutions. *Aptiv Solutions Acquires SRA Global Clinical Development*, CENTERWATCH NEWS ONLINE (Oct. 6, 2011), http://www.centerwatch.com/news-online/article/2325/aptiv-solutions-acquires-sra-global-clinical-development#sthash.peTIHxjd.dpuf. In 2014, ICON, a publicly traded CRO based in Ireland, acquired Aptiv Solutions. Press Release, ICON, *ICON Completes Acquisition of Aptiv Solutions* (May 8, 2014), http://www.iconplc.com/news-events/news/icon-completes-acquisitio-1/index.xml.

[191] INC Research had a private equity owner in 2011 when it acquired Kendle. Miller, *supra* note 188. In 2014, INC Research went public after failing to make a profit from 2011 to 2013. Jason deBruyn, *Leading to IPO, INC Research Has Only Recently Turned a Profit*, TRIANGLE BUS. J. (Oct. 9, 2014), http://www.bizjournals.com/triangle/news/2014/10/09/ipo-inc-research-turns-profit.html. For example, to "pay outstanding debt" from its private equity years, Quintiles went public in May 2013 after being held as a private company for approximately 10 years. *See* Laura Oleniacz, *Quintiles exec "very pleased" with IPO reception*, THE HERALD SUN (May 10, 2013, 2:27 PM), http://www.heraldsun.com/news/x383681051/Quintiles-exec-very-pleased-with-IPO-reception.

[192] Jason deBruyn, *PRA Health Sciences Readies to Go Public This Week*, TRIANGLE BUS. J. (Nov. 10, 2014), http://www.bizjournals.com/triangle/news/2014/11/10/pra-health-sciences-raleigh-readies-to-go-public.html.

[193] Miller, *supra* note 188, at 19.

[194] Erin Zureick Dunn, *$3.9-Billion Deal for PPD a Wise Move, Analysts Say*, STAR NEWS ONLINE (Oct. 3, 2011), http://www.starnewsonline.com/article/20111003/ARTICLES/111009958?p=2&tc=pg. "Many [CROs] have chosen private equity in order to get out from under public market scrutiny and visibility." Kenneth A. Getz, *Private Equity: Reshaping the CRO Landscape*, APPLIED CLINICAL TRIALS (Sept. 1, 2011), http://www.appliedclinicaltrialsonline.com/private-equity-reshaping-cro-landscape?pageID=2.

[195] U.S. DEP'T OF JUSTICE et al., *supra* note 173, at 43.

bribe had been made.[196] A privately held CRO, however, may be able to hide noncompliant behavior from the DOJ because, unlike a public company, it is not required to comply with the SOX's reporting and corporate governance requirements.[197]

Under Section 404 of SOX, large companies must testify "to the effectiveness of the company's internal control over financial reporting," and the CEO and CFO must disclose in annual reports "the effectiveness of 'disclosure controls' and whether there are any significant changes in internal controls since the date of the most recent evaluation of the internal controls was made."[198] The DOJ has stated, "These internal controls include those related to illegal acts and fraud—including acts of bribery—that could result in a material misstatement of the company's financial statements."[199] A privately held CRO, however, does not have to follow SOX and publicly disclose "any material weakness" in the internal auditor's report or have an "external auditor's report on internal control."[200] Thus, privately held CROs are in a better position than publicly traded CROs to shield their accounts from government investigations.

Given that the DOJ often relies on voluntary disclosures to pursue FCPA cases and, as shown above, a private company's public disclosure of fraud is not required in certain circumstances, the chances of the DOJ being able to detect fraudulent transactions, such as a CRO paying off a foreign government official, are slim at best.[201] Furthermore, CROs that operate on an international basis and that voluntarily disclose FCPA violations are at risk of the investigation broadening to their operations in other nations.[202]

Finally, the FCPA has a five-year statute of limitations.[203] As a result, the DOJ may have trouble bringing enforcement actions against companies that were held by private-equity companies for more than five years but are now publicly traded.[204] Due to the current market status of many CROs, the

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[196] U.S. DEP'T OF JUSTICE et al., *supra* note 173, at 39.

[197] *Sarbanes-Oxley Act Section 404: The Impact on Business*, NEW YORK UNIVERSITY STERN SCHOOL OF BUSINESS 2 (May 2, 2005), https://www.stern.nyu.edu/sites/default/files/assets/documents/uat_024646.pdf.

[198] GARY M. BROWN, DRAFTING SECURITIES FILINGS 2011: REGISTRATION, PERIODIC REPORTING AND DISCLOSURE UNDER THE SECURITIES EXCHANGE ACT OF 1934: WHAT A PUBLIC COMPANY SHOULD KNOW 21 (CMG Life Services Inc. 2011).

[199] U.S. DEP'T OF JUSTICE et al., *supra* note 173, at 42.

[200] *Id.*

[201] *See* Lucinda A. Low et al., *The Uncertain Calculus of FCPA Voluntary Disclosures*, THE AMERICAN BAR ASSOCIATION LLP 1 (2007), http://apps.americanbar.org/intlaw/spring07/World%20Bank%20Anticorruption%20Programs/Low%20-%20The%20Uncertain%20Calculus%20of%20FCPA%20Voluntary%20Disclosures.pdf.

[202] *Id.*

[203] U.S. DEP'T OF JUSTICE et al., *supra* note 173, at 34-35.

[204] Peter Henning, *Taking Aim at the Foreign Corrupt Practices Act*, N.Y. TIMES (Apr. 30, 2012, 1:55 PM), http://dealbook.nytimes.com/2012/04/30/Taking-aim-at-the-foreign-corrupt-practices-act/ ("Foreign bribery can take years to come to the government's attention, so the five-year statute of limitations can preclude prosecuting those involved in the payments").

DOJ may have little luck unless it revises its enforcement strategies. Given that FDA guidance documents allow for a sponsor to transfer responsibility and authority to a CRO on the management of a human subjects clinical trial, the federal government should have all anticorruption tools at its disposal if there is any malfeasance in such management.

In 2012, the DOJ successfully filed a suit against Biomet, a publicly traded medical device company, for numerous FCPA violations. Several of the charges involved corruption in the clinical trials Biomet was running in China.[205] Biomet subsequently settled with the DOJ and the SEC.[206] During the time of the illegal activity, Biomet was publicly traded on NASDAQ and, thus, required to file reports with the SEC.[207] In 2007, however, a group of private-equity firms took Biomet off the market for $11.4 billion.[208] Nevertheless, the Biomet case demonstrates that the DOJ can prosecute fraud related to overseas clinical trials when it is able to access certain company files.

The case is also notable because Biomet's status as a medical device company meant that, unlike a pharmaceutical company, it could not transfer responsibility for its study to a CRO. Currently, the FDA's Investigational Device Exemption "regulations do not permit a sponsor conducting a foreign clinical trial to transfer responsibility for device studies to a CRO.[209] The sponsor may contract with a CRO, but the sponsor will retain full responsibility for compliance with FDA requirements."[210] Thus, Biomet's status as a publicly traded medical device company made it more vulnerable to regulatory action than a pharmaceutical company that is able to transfer responsibility for a trial to a privately owned contract research organization.

The obstacles the DOJ faces should be considered along with how limited the FDA is in the corrective actions it can take. According to the FDCA, the FDA is able to issue warning letters, have meetings, conduct "reinspection[s] to verify promised corrective actions," and place the trial on clinical hold.[211] The most serious of their actions is to withdraw approval of an

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[205] U.S. DEP'T OF JUSTICE, DEFERRED PROSECUTION AGREEMENT, 19-20 (Mar. 26, 2012), http://www.justice.gov/criminal/fraud/fcpa/cases/biomet/2012-03-26-biomet-dpa.pdf.

[206] Richard Cassin, *Biomet Pays $22.8 Million to Settle Bribe Charges*, THE FCPA BLOG (Mar. 26, 2012, 12:08 PM), http://www.fcpablog.com/blog/2012/3/26/biomet-pays-228-million-to-settle-bribe-charges.html#sthash.nItqwT3Y.dpuf.

[207] DEFERRED PROSECUTION AGREEMENT, *supra* note 205, at 14.

[208] Cassin, *supra* note 206.

[209] Eve M. Brunts et al., *The International Clinical Trials Roadmap: Steering Clear of Legal and Practical Roadblocks*, 5 J. HEALTH & LIFE SCI. L. 1, 8 (June 2012). *See generally* COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, *supra* note 80, at Part II, 1.

[210] Brunts et al., *supra* note 209, at 8.

[211] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399f (2012). *See also* COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, *supra* note 80, at Part V, 1-2.

NDA.[212] This is rarely done; instead, the OIG found that the FDA "relies on voluntary compliance to correct violations of regulatory significance."[213]

In the United States, the FDA is able to issue injunctions and prosecute under federal statutes[214] and the FDCA.[215] Yet, it is debatable whether the FDCA gives the FDA extraterritorial enforcement powers.[216] The FDA has cited concerns about sovereignty before. Specifically, in response to the HHS OIG's recommendation that it encourage sponsors to file an IND, the FDA stated, "Under FDA's existing statutory authority, the Agency cannot require sponsors to file an IND for studies conducted overseas. In its oversight activities of clinical trials, the Agency must also be respectful of the sovereignty of individual countries and consider the role of national regulatory authorities."[217] Without a clear extension of statutory authority from Congress, the FDA cannot adequately enforce its regulations overseas. Instead, the FDA will continue to rely on foreign powers to ensure clinical trials are run properly.

IV. THE FDA HAS YIELDED REGULATORY DUTIES TO LOCAL GOVERNMENTS OVERSEAS WITH UNCERTAIN RESULTS

The FDA's lack of oversight of commercialized foreign clinical trials also should be considered in the context of how overseas trials are overseen by local authorities. The FDA relies heavily on local regulatory bodies to protect the integrity of the data and to ensure that the rights of the human subjects are protected. Trial review by IRBs, also known as IECs, is a central tenet of conducting trials in the United States. The review process theoretically has been exported abroad due to the International Conference of Harmonization (ICH). This part provides an overview of the ICH and its shortcomings, followed by a discussion of where overseas trials are located today, as well as a case study of how the ICH's requirements work in South Africa. Although the

[212] COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, *supra* note 80, at Part V, 2.

[213] 2001 HHS IG REPORT, *supra* note 178, at 14. For example, as mentioned previously, the FDA sent Pfizer a warning letter for the "inadequate monitoring" of a pediatric study that led to the overdosing of human subjects. Ball, *supra* note 135. The FDA noted that it had conveyed similar concerns to Pfizer before. *See id.* ("This is a repeat violation of findings communicated to you in an untitled letter generated after an April 25, 2005 to June 6, 2005 inspection of Pfizer's monitoring of clinical investigations for (b)(4).").

[214] 18 U.S.C. §§ 2, 371, 1001, & 1341 (2012).

[215] *See* COMPLIANCE PROGRAM GUIDANCE MANUAL, SPONSORS, *supra* note 80, Part V.

[216] *See* DuBois, *supra* note 11, at 189-90 (arguing that the FDCA does not explicitly state that Congress intended the FDA's regulatory authority to be applicable abroad). However, he argues that the FDCA does allow the FDA to act overseas in some cases. *Id.* He cites the "mission of the FDA is to … participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements," but he also argues that this only allows the FDA to work with foreign governments and that it does not necessarily allow the FDA to enforce the provisions of the FDCA overseas. *Id.*

[217] 2010 HHS IG REPORT, *supra* note 10, at 39.

ICH technically has set an international standard for good clinical practices, serious questions remain about adherence.

The FDA, along with industry entities, played a crucial part in starting the ICH as international trials became more common.[218] Six representative parties from the United States, Japan, and the European Union (EU) founded the ICH.[219] The industry representatives for the EU, Japan, and the United States are the major pharmaceutical trade associations: Japan Pharmaceutical Manufacturers Association, European Federation of Pharmaceutical Industries and Associations, and the Pharmaceutical Research and Manufacturers of America.[220]

The ICH set up international standards and a guideline for good clinical practice, which was adopted by the regulatory bodies of the EU, Japan, and the United States in the late 1990s.[221] Crucially, the ICH's good clinical practices (GCP) guidelines "provide a unified standard for the European Union[,] … Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions,"[222] allowing for foreign clinical trial data to be "transferable and acceptable to regulatory bodies in these major markets."[223] Thus, although one of the ICH's stated goals was to prevent duplicative testing, [224] it also instigated more foreign clinical trials being done outside these jurisdictions.

The ICH states that GCP is the standard for how a trial should be modeled, conducted, documented, and reported.[225] According to the ICH, the GCP standard ensures that the clinical data yielded are reliable and that the welfare of trial subjects is safeguarded.[226] The guideline for GCP also sets standards for how IRBs should be run.[227] In conjunction, as mentioned earlier, the FDA states that clinical studies conducted abroad under an IND must follow the FDA's IRB and informed consent requirements.[228]

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[218] WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 24.

[219] *Current Members and Observers*, ICH, http://www.ich.org/about/membership.html (last visited Aug. 9, 2016),

[220] *Id.*

[221] James R Dixon, Jr., *The International Conference on Harmonization Good Clinical Practice Guideline*, 6 QUALITY ASSURANCE: GOOD PRACTICE, REG. & L. 65, 69 (1999).

[222] Int'l Conf. on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *ICH Harmonised Tripartite Guideline—Guideline for Good Clinical Practice E6(R1)* 1 (1996), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

[223] WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 24.

[224] Caroline Nutley, *The Value and Benefits of ICH to Industry*, INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOC. 1, 2 (2000), http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Vision/Value_Benefits_for_Industry_2000.pdf.

[225] Int'l Conf. on Harmonisation of Technical Requirements, *supra* note 222, at 1.

[226] *Id.*

[227] *Id.* at 9-12.

[228] U.S. FOOD & DRUG ADMIN., ACCEPTANCE OF FOREIGN CLINICAL STUDIES—INFORMATION SHEET, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126426.htm (last updated June 25, 2014).

Subsequently, the regulatory agencies of other countries agreed to comply with the ICH guidelines, such as setting up local ethical review boards (i.e., IRBs or IECs),[229] to gain "pharmaceutical investments."[230] However, the power their newly formed IRBs actually have is questionable.

For example, Brazil complied with the ICH in 1997 and set up a National Committee on Research Ethics but, for the first few years, many of the country's experts saw the boards as little more than "symbolic."[231] In a 2001 study, the HHS OIG stated that the FDA does not inspect IRBs, that foreign countries do not provide very much information on the IRBs' work, and that the FDA should not always rely on the statements of foreign investigators that they will protect trial participants' rights.[232] In addition, registration for foreign IRBs is voluntary.[233] The HHS OIG report cited the World Health Organization's and the National Bioethics Advisory Commission's concerns that the IRBs had "insufficient monitoring practices."[234] (The ICH also led to the rapid rise of CROs, discussed earlier, as more sponsors sought to export their trials.)

Despite concerns voiced in 2001 about poorly developed local regulatory bodies, almost 10 years later, the HHS OIG found the majority of trial sites and subjects are in foreign countries.[235] Though Western Europe is where 60% of foreign clinical trial sites are located and where 58% of subjects are registered, increasing numbers of clinical trials are located in less developed countries.[236] Central and South America, in particular, accounted for more than one quarter of human subjects registered in overseas trials, partly due to Peru.[237] When the OIG reviewed the FDA's data, they found that Peru was home to the "fourth largest subject enrollment" out of all of the countries in the world.[238] The OIG also found that the FDA conducted no inspections of Peruvian trial sites.[239] Another developing country increasingly hosting foreign clinical trials is South Africa.[240] Major contract research organizations

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[229] WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 37.
[230] Petryna, *supra* note 31, at 31.
[231] WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 159.
[232] 2001 HHS IG REPORT, *supra* note 178, at ii.
[233] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS (IRBS) FREQUENTLY ASKED QUESTIONS–IRB REGISTRATION 4 (July 2009), http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm171256.pdf.
[234] 2001 HHS IG REPORT, *supra* note 178, at ii.
[235] 2010 HHS IG REPORT, *supra* note 10, at ii.
[236] *Id.* at 11.
[237] *Id.* at 11-12.
[238] *Id.* at 15.
[239] *See id.*
[240] *See id.* at 31; *see also* Zachary Brennan, *Pfizer Selects South African Trial Sites for Partnership Program*, OUTSOURCING-PHARMA.COM (June 19, 2013), http://www.outsourcing-pharma.com/Clinical-Development/Pfizer-Selects-South-African-Trial-Sites-for-Partnership-Program; *see also* Dan Stanton, *South Africa Conducive Environment for Clinical Trials, says PSI*, OUTSOURCING-PHARMA.COM

are attracted to it because it contains drug-naïve and "compliant" patients, English is spoken, and recruitment is easy.[241]

A. A South Africa Case Study

In South Africa, the Medicines Control Council (MCC) oversees the conduct of clinical trials.[242] The MCC was established in 1966 but, like many of South Africa's regulatory bodies, it underwent an overhaul after the end of apartheid in South Africa.[243] Many of South Africa's original ethical guidelines were put into effect during the 1960s, [244] when the white-only National Party governed the country.[245] In 2003, South Africa's government emphasized that those who are vulnerable due to sociohistorical factors must be protected in clinical trials.[246] Similar to the FDA's IND process, the MCC examines clinical trial applications based on their medical, scientific, and ethical criteria.[247]

Today, the ethical standards are set by both the South African Constitution and the ICH's GCP guidelines.[248] The Constitution of the Republic of South Africa Act states that human subjects have the right not to be medically tested on "without their informed consent."[249] Testing that is done without a human subject's informed consent is deemed unscientific and unethical.[250] In line with the ICH's GCP guidelines specifying that there be a review by an ethics committee before a trial commences, South Africa requires a research ethics committee to "ensure that participants are protected in accordance with international standards and guidelines."[251] For example, the research ethics committee is asked to consider the investigator's qualifications and whether the study population is a vulnerable one, worthy of special protection.[252]

(July 31, 2013), http://www.outsourcing-pharma.com/Clinical-Development/S-Africa-Conducive-Environment-for-Clinical-Trials-says-PSI.

[241] *CROs in South Africa*, CLINPAGE (Jan. 7, 2008) http://www.clinpage.com/article/.

[242] *The Medicines Control Council*, DEPARTMENT: HEALTH REPUBLIC OF SOUTH AFRICA, http://www.mccza.com/about/default.asp.

[243] Paul Ruff, *Regulation and Funding of Medicines in South Africa*, ASCO DAILY NEWS (May 31, 2015) *available at* https://am.asco.org/regulation-and-funding-medicines-south-africa.

[244] Helen Epstein, *The Mystery of AIDS in South Africa*, N.Y. REVIEW OF BOOKS (July 20, 2000), http://www.nybooks.com/articles/2000/07/20/the-mystery-of-aids-in-south-africa/.

[245] *National Party (NP)*, ENCYCLOPEDIA BRITANNICA, http://www.britannica.com/EBchecked/topic/405219/National-Party-NP (last visited Apr. 11, 2016).

[246] C. Slack et al., *Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research*, SOUTH AFRICAN MEDICAL RESEARCH COUNCIL 4 (2003), http://www.mrc.ac.za/ethics/ethicsbook5.pdf.

[247] *The Medicines Control Council, supra* note 242.

[248] *Information about the Rights of Clinical Trial Participants*, DEPARTMENT: HEALTH REPUBLIC OF SOUTH AFRICA, http://www.sanctr.gov.za/YourRights/tabid/185/Default.aspx (last visited Apr. 11, 2016).

[249] *Your Constitutional Rights*, DEPARTMENT: HEALTH REPUBLIC OF SOUTH AFRICA, http://www.sanctr.gov.za/Yourconstitutionalrights/tabid/198/Default.aspx (last visited Apr. 11, 2016).

[250] *Id.*

[251] *Research Ethics Committees*, DEPARTMENT: HEALTH REPUBLIC OF SOUTH AFRICA, http://www.sanctr.gov.za/YourRights/ResearchEthicsCommittees/tabid/178/Default.aspx (last visited Apr. 11, 2016).

[252] *Id.*

Many clinical trial applications are approved by the MCC each year.[253] However, South Africa's approval process is still a work in progress. Currently, the MCC's conflict of interest policy considers being a principal investigator or an investigator "in a clinical trial of relevance to the MCC's or Expert Committee's mandate" as only an indirect interest in a company, as opposed to a direct interest.[254] An indirect interest is deemed to be only an "intermediate risk level" rather than the "highest risk level" of a direct interest.[255] Whereas a direct interest can lead the MCC to restrict one's involvement in the MCC's affairs, when there is an indirect interest, the Council works "to balance limiting involvement in the council's activities and accessing the best expertise on a particular scientific matter."[256] South Africa's lower conflict of interest standards for the MCC may be due to a lack of qualified medical personnel and, thus, a willingness to embrace experts, even those with conflicts.[257]

Furthermore, South Africa's ethics committee structure was overhauled in April of 2000, because of concerns about improperly run trials.[258] In 2000, the American pharmaceutical company Triangle was ordered to halt its antiretroviral drug trial following the deaths of five patients.[259] There were concerns about whether informed consent was given[260] and how Triangle's CRO, Clindipharm, operated.[261] One contributor found that there was a lack of accountability among the CRO, the Ethics Committee, and the MCC; specifically:

> Professor Falkson, the head of the Ethics Committee at the University of Pretoria, had told me that Clindipharm was responsible for following up adverse events. Clindipharm, in turn, had told me that they referred all reports of adverse events to the Medicines Control Council, and now the head of the Medicines Control Council was telling me she refers them back to the Ethics Committee. The responsibility seemed to have gone full circle.[262]

However, although South Africa's clinical trial review process is a work in progress, the country is a democracy. In contrast, other countries where clinical trials have been outsourced do not have functioning democracies and

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[253] Ruff, *supra* note 243.
[254] *Policy on Management of Potential Conflict of Interest*, MEDICINES CONTROL COUNCIL 3 (Nov. 2011), http://www.mccza.com/documents/0979774eConflict_of_Interest_Nov11_v1_1.pdf.
[255] *Id.* at 4.
[256] *Id.* at 3.
[257] Miller, *supra* note 43.
[258] Pat Sidley, *South Africa to Tighten Control on Drug Trials After Five Deaths*, 320 BRIT. MED. J. 1028, 1028 (2000).
[259] *Id.*
[260] *Id.*
[261] Epstein, *supra* note 244.
[262] *Id.*

have questionable human rights records.[263] Notably, China and Russia, both of which lack impartial legal systems, are seeing a rise in foreign clinical trials.[264]

Although it has been more than a decade since the ICH came into being, even fully developed IRBs in non-democratic countries may not be truly independent and able to protect research participants or the integrity of the data.[265] In its 2010 report, the OIG found that the FDA did no inspections of Russian or Chinese clinical trial sites.[266] Thus, the FDA's deferment of regulatory authority to its foreign counterparts is a questionable move at best. In order for the FDA to have confidence that human subjects are protected in overseas clinical trials and that the data are sound, it will need to improve its ability to inspect overseas trials run under ICH guidelines.

CONCLUSION

Recognizing that there are gaps in its oversight of foreign clinical trials, the FDA has tried to improve its monitoring abilities. Nevertheless, it will need Congressional support in order to be successful. In 2006, the FDA launched a Bioresearch Monitoring Initiative[267] "to modernize and strengthen the agency's oversight and protection of subjects in clinical trials and the integrity of resulting data … and to assess compliance with FDA's regulations governing the conduct of clinical trials, including those for informed consent and ethical review."[268] As part of this initiative, the FDA has proposed a rule

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[263] *See* Wilson, *supra* note 61, at 665-66.

> Though some might claim that unforeseen medical complications are to be expected and should be addressed by legal recourse, the response fails to account for the lack of a comprehensive court system in less-developed countries. And, even with access to a semi-functioning legal system, it is unclear to what extent the governments of such countries will aid their citizens, since it is often the government who solicits pharmaceutical research.

Id. See also WHEN EXPERIMENTS TRAVEL, *supra* note 51, at 38 (stating that the approach of relying on local committees to "prevent inappropriate research … presupposes a working and fair legal system").

[264] Gareth Macdonald, *International, Multicentre Trial Approvals Soar in Russia in 2011*, OUTSOURCING-PHARMA.COM (Mar. 1, 2012), http://www.outsourcing-pharma.com/Clinical-Development/International-multicentre-trial-approvals-soar-in-Russia-in-2011; *see also* Zachary Brennan, *Pfizer to Shutter Clinical Research Unit in Singapore*, OUTSOURCING-PHARMA (Feb. 11, 2013), http://www.outsourcing-pharma.com/Clinical-Development/Pfizer-to-Shutter-Clinical-Research-Unit-in-Singapore; Dan Stanton, *Rise of Russia as EMA Reports Global Stretch of Clinical Trials*, OUTSOURCING-PHARMA.COM (Apr. 15, 2013), http://www.outsourcing-pharma.com/Clinical-Development/Rise-of-Russia-as-EMA-Reports-Global-Stretch-of-Clinical-Trials.

[265] Petryna, *supra* note 31, at 31.

[266] 2010 HHS IG REPORT, *supra* note 10, at 33.

[267] 2010 HHS IG REPORT, *supra* note 10, at 37.

[268] FDA's HSP/BIMO INITIATIVE ACCOMPLISHMENTS, U.S. FOOD & DRUG ADMIN. 1 (Sept. 2010), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM226424.pdf.

on Reporting Information Regarding Falsification of Data.[269] The FDA also plans to reprioritize how it selects clinical investigators for inspection.[270] To that end, the FDA "is piloting a tool that [will use] a risk-based prioritization process model" and is expected to allow CDER the ability to focus on ongoing studies, a shift from current practice, which would provide the opportunity for corrective actions to still be taken, "minimiz[ing] risks to subjects and preserv[ing] the integrity of the clinical trial."[271] How far the FDA is able to proceed with its initiative depends on whether it is able to secure adequate funding.

In 2011, the FDA met with pharmaceutical industry representatives, including representatives from the industry's trade organizations, Pharmaceutical Research and Manufacturers of America and BIO, to discuss the renewal of the Prescription Drug User Fee Act (PDUFA). Every five years, the FDA meets with the industry to negotiate the user fees that the industry pays directly to the FDA to "expedit[e] the drug approval process."[272] During the PDUFA V reauthorization, the FDA put forth a "proposal to improve human subject protection in clinical trial oversight,"[273] citing the 2010 OIG report.[274] The industry, however, "questioned the appropriateness of this proposal in the context of PDUFA discussions" and rejected the FDA's argument that "the agency's clinical trial oversight responsibilities are a part of the human drug review process that is partially funded by PDUFA."[275] One month later, the industry stated "that clinical trial sponsorship and oversight is an important responsibility of its member companies and … that it is currently meeting that responsibility to an appropriate standard."[276] Ultimately, the FDA's human subject protection proposal was not included in the final negotiated package approved by Congress.

Given the pharmaceutical industry's reluctance to fund FDA inspections for outsourced trials, the FDA is dependent upon the Congressional appropriations process. In addition to adequately funding the FDA, Congress should

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[269] *Id.* at 2.

[270] *Id.* at 4.

[271] *Id.*

[272] *PDUFA Legislation and Background*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm144411.htm (last updated Dec. 16, 2015).

[273] FDA–INDUSTRY PDUFA V REAUTHORIZATION MEETING, FINANCIAL SUB-GROUP, U.S. FOOD & DRUG ADMIN. 3 (Jan. 18, 2011), http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM243904.pdf.

[274] FDA Presentation, Stakeholder Meeting on PDUFA V Reauthorization, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM252925.pdf (Feb. 28, 2011) (powerpoint presentation on file with the author).

[275] FDA–INDUSTRY PDUFA V REAUTHORIZATION MEETING, *supra* note 273, at 3.

[276] U.S. Dep't of Health & Human Serv. et al., FDA–Industry PDUFA V Reauthorization Meeting, 3 (Feb. 10, 2011), http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM252933.pdf.

mandate that the FDA directly regulate the CRO industry. The FDA should investigate how sponsors and CROs interact. A list of which CROs contract with pharmaceutical sponsors should be publicly available information posted on clinicaltrials.gov, which is a service of the United States National Institutes of Health.[277] In addition, sponsors should be required to disclose whether a proposal to run a study was rejected by one CRO but accepted by another CRO. This would expose whether sponsors proposing poor protocols are still able to run the study—as long as a CRO, albeit a riskier one, is willing to accept the contract. Fines for not reporting such information should take into account that both pharmaceutical sponsors and contract research organizations are key players in a billion-dollar industry. Finally, Congress should examine the FDA's statutory authority overseas and reassess whether it can pursue meaningful enforcement actions.

Any reforms Congress and the FDA put forward will impact the conduct of clinical trials on a global level. Due to a privatized health care system, Americans spend more than $300 billion on pharmaceuticals each year, making the United States one of the largest, if not the largest, markets in the world.[278] As a result, the pharmaceutical industry cannot afford to bypass the American market. If Congress and the FDA were to use their leverage and put forth meaningful reforms, CROs and sponsors would have to change their practices.

Following his apology to the Guatemalan people, President Obama asked the Presidential Commission for the Study of Bioethical Issues to investigate how human subject protection standards in medical research should be improved.[279] President Obama directed the Commission to reexamine both international standards as well as current United States law as part of its review.[280] In order for the Commission to be truly effective, like the FDA and Congress, it must consider the full nature of how clinical trials are run today. Not only are they conducted predominately overseas but they are run by commercial entities that are able to evade regulatory oversight. Without serious consideration of these two factors, any proposed domestic reforms of the clinical trial process will fail.

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[277] *See* https://clinicaltrials.gov. *See also* Wilson, *supra* note 61, at 673-75 (giving a detailed recommendation on how an international registry that includes CROs' relationships with sponsors could be created).

[278] *Drug Costs to Rise as Much as 4 Percent in Hospitals, Clinics in 2013*, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS (Feb. 15, 2013), http://www.ashp.org/menu/AboutUs/ForPress/PressReleases/PressRelease.aspx?id=739.

[279] President's Bioethics Commission Names International Research Panel, PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES (Mar. 1, 2011), http://bioethics.gov/cms/node/13. *See also "Ethically Impossible" STD Research in Guatemala from 1946 to 1948*, PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES (Sept. 2011), http://bioethics.gov/sites/default/files/Ethically%20Impossible%20%28with%20linked%20historical%20documents%29%202.7.13.pdf.

[280] *Id.*