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Can the FDA Improve Oversight of Foreign Clinical Trials?: Closing the Information Gap and Moving Towards a Globalized Regulatory Scheme

*André Ourso**

In June 2010, national news sources reported on a recently released government report concerning the Food and Drug Administration's (FDA) ability to monitor foreign clinical trials used to support marketing applications for pharmaceutical products sold in the U.S.¹ The report was prepared by the Office of Inspector General of the Department of Health and Human Services (OIG), and found that for the fiscal year 2008, 80% of approved marketing applications for drugs and biologics contained data from foreign clinical trials.² In 2008, 78% of all subjects who participated in clinical trials were enrolled at foreign sites, and over 54% of all clinical trial sites were located outside the United States.³ The report also indicated that the FDA faced challenges to conducting foreign inspections and data limitations inhibited the agency's ability to monitor foreign clinical trials.⁴ The report found that the FDA inspected just 0.7% of foreign clinical trial

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1. See generally Gardiner Harris, *Concern Over Foreign Trials for Drugs Sold in U.S.*, N. Y. TIMES (Jun. 21, 2010), http://www.nytimes.com/2010/06/22/health/research/22trial.html?_r=1&hpw; Laura Strickler, *Report Raises Concern Over Foreign Drug Trials*, CBS NEWS (Jun. 22, 2010), http://www.cbsnews.com/8301-31727_162-20008510-10391695.html.

2. OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUM. SERVS., OEI-01-08-00510, CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS 10 (2010) [hereinafter OIG, CHALLENGES], <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf> (reporting: (1) to determine the extent to which sponsors submitted data from foreign clinical trials to support drug and biologic marketing applications by the FDA in fiscal year 2008 and (2) to determine the extent to which the FDA monitors and inspects foreign clinical trials that support marketing applications).

3. *Id.*

4. *Id.* at 17.

sites.⁵ This report is not the first time that the OIG has addressed concerns about FDA's oversight of clinical trials and foreign clinical trials.⁶

Pharmaceutical companies' utilization of data from foreign clinical trials to support marketing applications for drugs sold in the U.S. is not a recent result of the phenomenon of globalization. The emergence of foreign clinical trials began almost two decades ago.⁷ From 1990 to 1999, the number of foreign clinical investigators conducting drug research under Investigational New Drug Applications (IND) increased sixteen-fold.⁸ From 1998 to 2008, the percentage of foreign clinical investigators conducting clinical trials under INDs has more than doubled.⁹ Presently, sponsors' utilization of foreign clinical trial data is ubiquitous and commonly considered an indispensable aspect of gaining drug approval.¹⁰ A recent study, searching the ClinicalTrials.gov website, found that the twenty largest U.S. based pharmaceutical companies were conducting one-third of their clinical trials exclusively at foreign sites.¹¹

There are several reasons for the movement of clinical trials overseas, especially to developing countries. Pharmaceutical companies can substantially save costs conducting trials in developing countries.¹² A first-rate academic medical center in India may charge one-tenth the cost a second-tier medical center in the U.S. would charge.¹³ A decrease in volunteers for clinical trials in the U. S. is also contributing to the shift of trials overseas.¹⁴ Volunteers in the U.S. are scarce because Americans are

5. *Id.* at 15.

6. See OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUM. SERVS., OEI-01-00-00190, THE GLOBALIZATION OF CLINICAL TRIALS: A GROWING CHALLENGE IN PROTECTING HUMAN SUBJECTS, (2001) [hereinafter OIG, THE GLOBALIZATION OF CLINICAL TRIALS]; OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUM. SERVS., OEI-01-06-00160, THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL TRIALS (2007).

7. OIG, THE GLOBALIZATION OF CLINICAL TRIALS, *supra* note 6, at 6.

8. *Id.*

9. OIG, CHALLENGES, *supra* note 2, at 13.

10. 21 C.F.R. § 312.3(b) (2011) ('Sponsor' means a person or entity who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization).

11. Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816, 816 (Feb. 19, 2009) (registering federally and privately supported clinical trials conducted in the United States and around the world, ClinicalTrials.gov provides information about a trial's purpose, who may participate, locations, and contact information. As a result of the FDA Modernization Act (FDAMA), Pub. L. No. 105-115, 111 Stat. 2296 (1997), the National Institute of Health (NIH), through its National Library of Medicine (NLM), developed the site in collaboration with the FDA, *About ClinicalTrials.gov*, NAT'L INST. OF HEALTH (last updated Apr. 2, 2008), <http://clinicaltrials.gov/ct2/info/about>).

12. *See id.*

13. *Id.*

14. SONIA SHAH, THE BODY HUNTERS: TESTING NEW DRUGS ON THE WORLD'S POOREST

more reluctant to join risky experiments.¹⁵ Developing countries may also have a higher prevalence of certain diseases, making clinical trials easier to organize.¹⁶ In addition, patients in developing countries with little exposure to medications make better subjects for clinical testing.¹⁷ For example, India is an appealing country for sponsors to conduct clinical trials because it has a genetically diverse population of over one billion people who have a myriad of diseases yet have not been exposed to many medications.¹⁸

Furthermore, conducting clinical trials globally shortens the timeline for clinical testing.¹⁹ A sponsor may have a larger pool of volunteers to enroll participants in trials in foreign and developing countries than in the U.S.²⁰ A larger pool of potential clinical trial participants, combined with the lower cost of research, accelerates recruitment.²¹ Cutting down the time and expense until a drug is approved and brought to market saves sponsors a significant amount of the total cost of drug development.²²

Another reason sponsors conduct clinical trials in foreign countries is because it may be a prerequisite to marketing approval in those countries.²³ Moreover, stronger intellectual property protections and the widespread adoption of certain international standards make drug approval more conducive and cost efficient in foreign countries, especially in those of the developing world.²⁴ Not surprisingly, many foreign clinical trials are conducted in developing nations.²⁵

Despite advantages in conducting clinical trials in developing countries, there is some skepticism regarding foreign clinical trials, including concerns about questionable data and verifying clinical results.²⁶ Foreign clinical trials also raise concerns about the ethical treatment of human subjects enrolled in these trials, particularly in countries where enforcement

PATIENTS 5 (2006).

15. Mary Flaherty, Deborah Nelson & Joe Stephens, *Testing Tidal Wave Hits Overseas*, WASH. POST, A1 (Dec. 18, 2000), <http://www.washingtonpost.com/wp-dyn/Content/article/2008/10/01/AR2008100101117.html> (addressing the issue of emerging international clinical drug trials and its ethical and safety implications in part two of a six part series entitled, *The Body Hunters*).

16. *Id.*

17. *Id.*

18. Samiran Nundy & Chandra Gulhati, *A New Colonialism? – Conducting Trials in India*, 352 NEW ENG. J. MED. 1633, 1634 (Apr. 21, 2005).

19. Glickman et al., *supra* note 11, at 816.

20. *Id.* at 817.

21. *Id.*

22. *Id.*

23. *Id.*

24. *Id.*

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

26. Strickler, *supra* note 1; *see also* Harris, *supra* note 1.

of regulation and human subject protection may be inadequate.²⁷ There may be an even greater risk of unethical treatment in developing countries where potential subjects are unaware of the notion of informed consent.²⁸

In the past, lack of trust has been focused on the government support and involvement in unscrupulous clinical studies, such as the infamous Tuskegee syphilis studies in the U.S., and the recently uncovered experiments on sexually transmitted diseases in Guatemala.²⁹ Today, there may be greater concern with multinational pharmaceutical companies

27. See Madhur Singh, *Should Clinical Trials Be Outsourced?*, TIME.COM (Aug. 7, 2008), <http://www.time.com/time/health/article/0,8599,1830334,00.html>.

28. Finuala Kelleher, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J.L. & SOC. PROBS. 67, 69 (2004-2005); see also Int'l Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, Good Clinical Practice, *Informed Consent of Trial Subjects* §4.8.10, ICHGCP.NET, <http://ichgcp.net/4-investigator> (establishing best practice on informed consent discussions and written forms to include information that; (a) the trial involves research, (b) The purpose of the trial, (c) The trial treatment(s) and the probability for random assignment to each treatment, (d) The trial procedures to be followed, including all invasive procedures, (e) The subject's responsibilities, (f) Those aspects of the trial that are experimental, (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant, (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this, (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks, (j) The compensation and/or treatment available to the subject in the event of trial-related injury, (k) The anticipated prorated payment, if any, to the subject for participating in the trial, (l) The anticipated expenses, if any, to the subject for participating in the trial, (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled, (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access, (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential, (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial, (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury, (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated, (s) The expected duration of the subject's participation in the trial, (t) The approximate number of subjects involved in the trial).

29. See generally Robert Bazell, *U.S. apologizes for Guatemala STD experiments*, NBC NEWS (Oct. 1, 2010, 7:05 PM), <http://www.msnbc.msn.com/id/39456324/> (citing two egregious instances involved the nonconsensual infection of syphilis or gonorrhea into patients. The studies were sponsored by the U.S. Public Health Service, and in the case of Guatemala, the Guatemalan government).

sponsoring unethical clinical trials.³⁰ There is also unease with independent contractors hired by sponsors to recruit and enroll potential patients overseas.³¹ These companies employ technicians who are paid to gather a certain number of human subjects and even conduct the clinical trials themselves.³² These contract research organizations (CROs) generate annual revenue of \$20 billion.³³

One notorious and egregious example of such trials was Pfizer's study of Trovan in Nigeria. In 1996, in the midst of a bacterial meningitis outbreak in Nigeria, Pfizer set up a medical camp in Kano where child victims of the outbreak could receive treatment and medication while allowing Pfizer to conduct clinical trials on its promising new antibiotic, Trovan.³⁴ Unbeknownst to the patients and their families, the non-profit aid group Medecins Sans Frontieres (Doctors Without Borders) set up a medical camp in the very same area prior to the arrival of Pfizer's team. Doctors Without Borders had been administering proven-effective antibiotics to patients free of charge.³⁵ Conflicts between the two groups arose, with Pfizer's team disrupting the existing triage system and co-opting the scarce resources.³⁶ After quickly conducting its trials, Pfizer left Kano without offering any long-term follow up care to its human subjects.³⁷

Pfizer reportedly enrolled many of the patients in the drug trial without obtaining the informed consent of either the subjects or their parents.³⁸ The FDA found inconsistencies in the data Pfizer submitted from the Kano trial, and, in 1999, post-marketing reports revealed a strong association between Trovan and an increased risk of acute liver failure.³⁹ In June 1999, the FDA issued a public health advisory concerning reports of liver toxicity and failure associated with the use of trovafloxacin.⁴⁰ The FDA advised

30. See Strickler, *supra* note 1.

31. See Bartlett & Steele, *supra* note 25.

32. *Id.*

33. *Id.*

34. Joe Stephens, *Where Profits and Lives Hang in the Balance*, WASH. POST, A1 (Dec. 17, 2000), <http://www.washingtonpost.com/wp-dyn/content/story/2008/10/01/ST2008100101390.html> (addressing ethical and safety implications of emerging international clinical drug trials. Part one of a six part series entitled, *The Body Hunters*, describes events surrounding Pfizer's testing of the antibiotic, trovafloxacin (sold by Pfizer as Trovan) on children in Nigeria suffering from meningitis).

35. *Id.*

36. *Id.*

37. *Id.*

38. *Id.*

39. Melody Petersen, *Unforeseen Side Effects Ruined One Blockbuster*, N.Y. TIMES (Aug. 27, 2000), <http://www.nytimes.com/2000/08/27/business/unforeseen-side-effects-ruined-one-blockbuster.html>.

40. Murray M. Lumpkin, M.D., *Food and Drug Administration 09 June 1999 Trovan*

physicians to limit use of trovafloxacin to certain seriously-ill patients.⁴¹ The Trovan studies raised serious concerns about the unethical treatment of human subjects, including lack of informed consent and lack of proper follow-up care.⁴² Government corruption and lack of oversight were also problems in Nigeria that presumably contributed to the controversy surrounding the studies.⁴³

While Pfizer's Trovan trial is a particularly shocking example, foreign clinical trials are commonly associated with concern over the ability of foreign regulatory bodies and institutional review boards to adequately monitor clinical trials to protect the rights, safety, and welfare of human subjects and ensure data integrity.⁴⁴ Sponsors' utilization of foreign clinical trials in which unethical treatment of human subjects occurs, or where tainted data is used to support drug marketing applications, may pose a significant danger to patients' health and the integrity of scientific research.⁴⁵

I. FDA REGULATION OF FOREIGN CLINICAL TRIALS

Pharmaceutical and biotech companies interested in marketing a drug or biologic in the U. S. must first submit a marketing application to the FDA.⁴⁶ The Federal Food, Drug, and Cosmetic Act requires all new investigational drugs to undergo clinical trials on human subjects which demonstrate the safety and efficacy of these products prior to their approval for marketing.⁴⁷ Sponsors must submit clinical trial results with their marketing applications.⁴⁸ The FDA generally bases its approval to market a new drug

(*Trovafloxacin/Alatrofloxacin Mesylate*), U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/UCM053103> (last updated Apr. 30, 2009).

⁴¹ *Id.*

42. See Stephens, *supra* note 34.

43. See *id.*

44. OIG, CHALLENGES, *supra* note 2, at 2.

45. See Glickman et al., *supra* note 11, at 817.

46. 21 C.F.R. § 314.50 (2011) (governing New Drug Application (NDA) for drugs); 21 C.F.R. § 601.2 (2011) (governing Biologic Licensing Application (BLA) for a biologic).

47. Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-399a (2004)).

48. 21 C.F.R. § 314.50(d)(5) (2011); 21 C.F.R. § 312.21 (2011) (including information from all phases of clinical trials. Phase I includes the initial introduction of an investigational new drug into humans, Phase I studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase II includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the

on pivotal Phase III trials.⁴⁹ However, the agency considers all clinical trials when evaluating the safety and efficacy of a drug.⁵⁰

An Investigational New Drug Application (IND) provides an exemption to federal law that prohibits unapproved drugs and biologics from being introduced into interstate commerce.⁵¹ Sponsors intending to conduct clinical trials in the U.S. must submit an IND to the FDA prior to starting research.⁵² FDA authority to oversee clinical trials begins when a sponsor submits an IND to the agency.⁵³ The FDA reviews the IND for safety to ensure that subjects are not exposed to unreasonable risk.⁵⁴ Sponsors may conduct foreign clinical trials under an IND, but because interstate commerce laws do not extend to foreign countries the IND is unnecessary for clinical trials conducted outside the U.S.⁵⁵

The FDA allows sponsors to submit marketing applications with data from foreign clinical trials not conducted under an IND.⁵⁶ Sponsors may also submit results of earlier foreign clinical trials not conducted under an IND to support a current IND.⁵⁷ If a sponsor wants to submit data from foreign clinical trials not conducted under an IND, the sponsor must conduct the trials in accordance with Good Clinical Practice (GCP).⁵⁸ FDA regulations require sponsors to submit a description of the actions the

drug. Phase II studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects. Phase III studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase III studies usually include from several hundred to several thousand subjects. Phase III trials are the most pivotal trials, evaluating the “overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.”)

49. OIG, CHALLENGES, *supra* note 2, at 3.

50. *Id.*

51. 21 U.S.C.A. § 355(i) (West 2010); 42 U.S.C.A. § 262(a) (West 2010).

52. 21 C.F.R. § 312.20 (2011).

53. OIG, CHALLENGES, *supra* note 2, at 3.

54. 21 C.F.R. § 312.20 (2011); 21 C.F.R. § 312.40 (2011); 21 C.F.R. § 312.42 (2011) (ensuring INDs provide information on the clinical trial protocol, the qualifications of trial personnel, and assurances that investigators will protect research subjects' welfare³).

55. OIG, CHALLENGES, *supra* note 2, at 3.

56. 21 C.F.R. § 312.120 (2011); 21 C.F.R. § 314.106 (2011).

57. 21 C.F.R. § 312.23(b) (2011).

58. 21 C.F.R. § 312.120(a)(i) (2011); *see also* INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, Guideline for Good Clinical Practice, E6(R1), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf (last visited September 13, 2011) (describing that Good Clinical Practices document the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. The GCP also covers aspects of monitoring, reporting and archiving of clinical trials).

sponsor or applicant took to ensure that the research conformed to GCP.⁵⁹ The information provided in the description is similar to the information provided in an IND.⁶⁰

The FDA also requires certain clinical trials to be registered in the publicly accessible databank, ClinicalTrials.gov.⁶¹ The Food and Drug Administration Amendments Act (FDAAA) extended and expanded the clinical trial registration requirements of the databank to include all “applicable clinical trials”.⁶² “Applicable clinical trials” are post-Phase I studies subject either to §505 of the FDCA, or §351 of the PHSA.⁶³ The FDAAA requires the sponsor of an applicable clinical trial to submit information for entry into the databank no later than twenty-one days after the first subject is enrolled.⁶⁴ Additionally, the FDAAA requires that the results of each applicable clinical trial be reported to the NIH for inclusion into the databank.⁶⁵

Besides an IND, GCP, and databank registry requirements, the FDA may conduct onsite inspections to ensure clinical investigators, sponsors, and independent review boards (IRB) comply with FDA regulations.⁶⁶ FDA authority to conduct inspections extends to both foreign and domestic sites.⁶⁷ Most inspections occur after the FDA receives a marketing application, but the Agency may choose to conduct an inspection while a clinical trial is ongoing.⁶⁸

II. ADDRESSING LIMITATIONS TO THE OVERSIGHT OF FOREIGN CLINICAL TRIALS

Despite seemingly extensive regulations governing the conduct of

59. 21 C.F.R. § 312.120(b) (2011).

60. *Id.*; see also 21 C.F.R. § 312.23(a) (2011) (detailing required IND content).

61. Food and Drug Administration Modernization Act, Pub. L. No. 105-115, §113, 111 Stat. 2296 (1997) (amending the FDCA, 21 U.S.C. § 301 et seq., and the Public Health Service Act (PHSA), 42 U.S.C. § 201 et seq.).

62. Food and Drug Administration Amendments Act, Pub. L. No 110-85, 121 Stat. 823 (2007) (amending sections of the FDCA, 21 U.S.C. § 301 et seq., § 402 of the PHSA, and 42 U.S.C § 282); see also NIH, DRAFT ELABORATION OF DEFINITIONS (2009), at 7, available at http://grants.nih.gov/Clinicaltrials_fdaaa/ (last visited November 22, 2010) (defining “applicable clinical trials” to generally include: *trials of drugs and biologics known as “applicable drug clinical trial”* and *trials of devices known as “applicable device clinical trial”*).

63. 42 U.S.C.A. § 282(j)(1)(A)(iii) (West 2011) (§ 505 of the FDCA codified as 21 U.S.C. § 355 and § 351 of the PHSA codified as 21 U.S.C. 262, governing the use of a drug or biologic prior to marketing and after approval).

64. 42 U.S.C.A. § 282(j)(2)(C)(ii) (2011).

65. *Id.*; 42 U.S.C.A. § 282(j)(3)(E)(ii) (2011).

66. 21 C.F.R. § 312.58 (2011); § 312.68 (2011).

67. OIG, CHALLENGES, *supra* note 2, at 4.

68. *Id.*

clinical trials and the submission of data, some significant issues arise out of the FDA's current regulatory scheme. These issues limit the FDA's ability to ensure the protection of human subjects and the integrity of clinical trial data. One issue is that the Agency is unable to account for all clinical trial information, because it often receives clinical trial information in a nonstandard format.⁶⁹ Additionally, the FDA is unaware of ongoing foreign clinical trials which are not conducted under an IND.⁷⁰ If the FDA is to effectively ensure the protection of research subjects and the quality of clinical trial data, the Agency must at least be aware of any and all foreign clinical trials that a sponsor may use to support a U.S. marketing application either before or shortly after those trials begin. Still, the FDA will not only have to know that these trials exist, it will need to compel production of complete and timely information so that the Agency may discern any risks associated with the trials.

For sponsors that conduct foreign clinical trials according to GCP, the FDA recommends that complete raw data sets of all clinical trials be submitted.⁷¹ Despite current guidelines, sponsors sometimes provide incomplete clinical study reports with missing information regarding site locations and subject enrollment.⁷² Furthermore, sponsors often submit data in nonstandard and inconsistent formats.⁷³ Nonstandard and missing data significantly complicate the FDA's ability to provide timely review of marketing applications.⁷⁴ A few months after the release of the OIG report the FDA issued a final rule amending its regulations governing safety reporting requirements for drugs and biologics subject to an IND.⁷⁵ The revised rule codified "the agency's expectations for timely review, evaluation, and submission of relevant and useful safety information" and implemented "internationally harmonized definitions and reporting standards."⁷⁶

The OIG report also recommended that the FDA require standardized electronic clinical trial data as well as the creation of an internal database to assist reviewers in effectively reviewing the data.⁷⁷ The FDA could simply create a rule to compel sponsors to submit standardized raw data. This rule would enable the FDA to ensure reviewers have all the information needed

69. *Id.*

70. *Id.* at 17-18.

71. *Id.* at 18.

72. *Id.*

73. OIG, CHALLENGES, *supra* note 2, at 19.

74. *Id.*

75. 75 Fed. Reg. 59, 935 (Sept. 29, 2010).

76. *Id.*

77. OIG, CHALLENGES, *supra* note 2, at 20.

to more effectively review the data.⁷⁸

Sponsors and investigators should welcome requirements for standardized data. Standardization of data would arguably make it easier for investigators or sponsors to address FDA reviewers' inquiries regarding a particular trial by enhancing communication of the parties through the use of one universally recognized form of communication. The efficiency associated with data standardization and an internal database could speed up the time needed to grant marketing approval, saving sponsors time and money. Consequently, increased standardization may have the effect of making foreign clinical trials even more desirable to sponsors. Regardless, even with better standardization requirements, the trend of increasing utilization of foreign clinical trials, including those not conducted under an IND, will inevitably continue.⁷⁹ At very least, by insisting that sponsors submit complete and standardized data, the FDA could begin to better evaluate foreign clinical trials and address potential and actual problems before they rise to the level of Kano.

An internal database of standardized data would also enable the FDA to more effectively select sites for inspection.⁸⁰ According to the FDA, efforts are currently underway by the Center for Drug Evaluation and Research (CDER), which serves to promote and protect the health of Americans by assuring that all prescription and over-the-counter drugs are safe and effective, to develop standards to be used in conducting a pilot program that will use the existing data submission framework, to request standardized data.⁸¹ The FDA also indicated that a more robust system for uniquely identifying individual clinical investigators is needed.⁸² Perhaps requiring such identifying information when sponsors initially register data could satisfy this need. In fact, in July 2011, the FDA issued an advanced notice of proposed rulemaking (ANPRM) "to seek comment on how to better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay and ambiguity for researchers."⁸³ The proposed changes to improve the current data collection system involve; 1) standardized, streamlined set of data elements, 2) a Federal-wide web-based portal to allow investigators to submit electronically certain pre- and post-market safety and have the data

78. *Id.*

79. *Id.* at 13.

80. *Id.* at 20.

81. *Id.*, at 38. (responding to the Inspector General's comments, FDA officials note that "if successful, the pilot [program] can be expanded to include all marketing applications with clinical data submitted to CDER and would enable more effective targeting of limited inspection resources . . .").

82. *Id.*

83. 76 Fed. Reg. 44,512 (July 26, 2011).

automatically delivered to the appropriate agencies and oversight bodies, 3) and harmonizing safety reporting guidance across all Federal agencies, including harmonizing terminology and clarifying scope and timing of such reports.⁸⁴ Whatever the ultimate method of collection, utilization of an internal database of robust, complete, and standardized registration and results data is an important step toward meaningful improvement in the efficient analysis of submitted data.

Still, any such requirements for standardized data and an internal database cannot be fully effective if the FDA is unaware of some ongoing foreign clinical trials. The OIG report indicated that sponsors are increasingly conducting early-phase foreign clinical trials without INDs.⁸⁵ Sponsors submit clinical trial results to support their marketing applications years after the start of trials.⁸⁶ Without an IND, in most cases, FDA is uninformed of ongoing foreign clinical trials until the trial data is submitted in support of a U.S. marketing application.⁸⁷ To further assess this situation, the OIG recommended that the FDA monitor trends in foreign clinical trials not conducted under an IND.⁸⁸ Retrospective analysis of data could help identify risks associated with these trial sites. As sponsors submit clinical trial results in conjunction with marketing applications, the FDA could assess whether subjects were exposed to increased risk and whether collected data were accurate and reliable.⁸⁹ In the event the FDA identified particular problems, the agency could use its authority to delay approval or disqualify data altogether.

However, even if reviewers did identify potential problems regarding adequate subject protection it would generally be too late to prevent the harm to which human subjects were exposed. Under current requirements it seems the FDA lacks the authority to concurrently monitor these ongoing trials.⁹⁰ Additionally, sponsors are not required to enter data into the registry mandated by the FDAAA for Phase I foreign clinical trials.⁹¹ This lack of oversight can be increasingly dangerous given that Phase I trials may pose greater risk for subjects because the products being researched have yet to be tested widely in humans, and represent the first opportunity for researchers to evaluate safety and side effects on living subjects.⁹² Surely, the FDA cannot be expected to adequately provide subject

84. *Id.*

85. OIG, CHALLENGES, *supra* note 2, at 17.

86. *Id.*

87. *Id.* at 17 and 18.

88. *Id.* at 20.

89. *Id.*

90. *Id.*

91. 42 U.S.C. § 282(j)(1)(A)(iii) (2011).

92. OIG, CHALLENGES, *supra* note 2, at 17.

protection when the Agency has no idea where foreign non-IND trials are taking place. This conundrum presents the questions: how does the FDA become aware of ongoing foreign clinical trials and how can it effectively ensure data quality and adequate human subject protection before the trial results data are submitted to support a marketing application?

In an effort to find a solution to this problem, the OIG recommended that the FDA encourage sponsors to either voluntarily consult with the FDA about clinical trial protocols or submit an IND.⁹³ An IND provides a level of FDA oversight before human subjects are enrolled. In the event that concerns are identified, the Agency would have the ability to prevent trials from starting, or require sponsors to adjust study protocol. After submission of an IND, the FDA also has the opportunity to conduct real-time inspections.⁹⁴ Encouragement of INDs submissions or voluntary consultations might work for some sponsors if they have an incentive to comply. Cooperating along these lines shows goodwill towards the FDA, potentially making it easier to resolve issues with the FDA if they arise. Also, by providing study information voluntarily before studies begin, the sponsor cuts down on the chances that a marketing application will be held up, thus minimizing potential delays in bringing the product to market.

The FDA could also provide other incentives to promote INDs.⁹⁵ However, before incentives are legislated, care should be taken to ensure that any such incentives will have the desired effect. Merely encouraging the submission of IND's seems like a rather conciliatory approach to trying to get a handle on the problems associated with foreign clinical trials. Despite incentives, some sponsors may still feel it is in their interests to only adhere to the current regulations. Although earlier assertions noted that widespread adoption of international standards may contribute to the increase in foreign clinical trials, sponsors may engage in a "race to the bottom," instead seeking out certain nations that have lax regulations or are known to largely ignore shortcuts around GCP standards. Sponsors may find that avoiding additional scrutiny may prove to be more beneficial than providing study information before submitting a marketing application to the FDA.

If the FDA wanted to monitor ongoing foreign clinical trials it should require sponsors to submit study information before research begins, similar to the effect of an IND. Such a rule would require registration of pre-trial data for any sponsor that anticipates marketing a drug in the U.S. using data from foreign clinical trials not conducted under an IND. However, there

93. *Id.* at 21.

94. *Id.*

95. *Id.*

would likely be significant pushback by industry against such requirements. It is also questionable whether the FDA has the authority to require this data.

NIH guidelines provide some clarification as to whether certain foreign clinical trials are considered “applicable drug clinical trials,” subjecting them to FDAAA registration and reporting requirements.⁹⁶ According to draft regulations, when a clinical investigation includes sites both within and outside the U.S., all trials included in the investigation are considered “applicable drug clinical trial[s].”⁹⁷ A clinical investigation conducted exclusively outside the U.S. is deemed an “applicable drug clinical trial” if the product is subsequently manufactured in the U.S.⁹⁸ Of course, foreign clinical trials conducted under an IND are deemed “applicable drug clinical trial[s].”⁹⁹ If all trial sites are outside the U.S., the trials are not conducted under an IND, and the drug is manufactured outside of the U.S., then the investigation is not considered an “applicable drug clinical trial.”¹⁰⁰ Consequently, these drugs are not subject to either §505 of the FDCA or §351 of the PHSA.¹⁰¹ However, the draft elaboration does not address the situation wherein foreign clinical trials are not conducted under an IND, the product is not manufactured in the U.S., but the sponsor subsequently seeks U.S. marketing approval.¹⁰² One could interpret that such a trial becomes subject to FDA requirements after the sponsor submits the marketing application with all clinical trial information, triggering the FDAAA’s registration obligations.¹⁰³ Because the study would only become subject to the registration requirements after the trial had already been completed, a sponsor or investigator could not meet the registration requirements within 21 days of the first subject’s enrollment.¹⁰⁴ Unless a sponsor anticipated that the trial would subsequently be used to support a U.S. marketing application and voluntarily submitted the information the sponsor could not comply with the registration timeline.¹⁰⁵

If this interpretation is correct, the FDA would need to clarify this ambiguity. It has been suggested that the FDA could carve out an

96. See Nat’l Insts. of Health, Draft, *Elaboration of Definitions of Responsible Party and Applicable Clinical Trial*, 4-10 (March 9, 2009), <http://prinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf>.

97. *Id.* at 8.

98. *Id.*

99. *Id.*

100. *Id.* at 7.

101. *Id.* at 8.

102. Carolyne R. Hathaway et al., *The Web of Clinical Trial Registration Obligations: Have Foreign Clinical Trials Been Caught?*, 64 Food & Drug L.J. 261, 269 (2009).

103. *Id.* at 269-70.

104. *Id.* at 270.

105. *Id.*

exception to the registration obligation that attaches to a foreign trial not conducted under an IND and using products not manufactured in the U.S. . The FDA could require registration of information that is only feasible when the study becomes an applicable clinical trial, thus eliminating the timeline requirement.¹⁰⁶ In the alternative, the FDA should require registration of study information to include these non-IND foreign clinical trials, thus compelling sponsors to anticipate whether they will use a foreign trial for subsequent U.S. marketing applications. The creation of such a rule would expand the FDA's oversight to ongoing non-IND foreign clinical trials, which do not use products manufactured in the U.S. This rule would be consistent with the clinical registry's stated purpose of increased transparency of clinical trials for products marketed in the U.S.¹⁰⁷ The FDA is currently assessing to what extent the ClinicalTrials.gov database could be used to obtain information on foreign clinical trials not conducted under an IND.¹⁰⁸ If a rule is not possible then new legislation would have to provide the FDA with the appropriate authority.

Expanding registration requirements to these non-IND foreign clinical trials would provide the FDA with more complete and current information to evaluate ongoing foreign clinical trials. However, paper reviews of data submissions required under something similar to IND may be considered fairly passive oversight. The real tool in the FDA's regulatory arsenal is its ability to conduct site inspections. New registration requirements combined with requirements for data standardization and a robust data management system would make monitoring trends and subsequent data analysis more effective in assessing risks associated with foreign clinical trials. Consequently, if the Agency utilizes the information to identify high risk trials, inspections of foreign clinical trial sites would be a more effective enforcement tool.

Regression analysis indicated that the Agency was sixteen times more likely to inspect a clinical investigation at a domestic site than a foreign site.¹⁰⁹ The OIG noted that FDA could inspect clinical trials in more countries, targeting trials in those countries that the agency has not previously inspected or where GCP standards have recently been adopted.¹¹⁰ Inspecting more sites would require more resources, yet resource constraints already limit the number of foreign clinical trial site inspections.¹¹¹ In addition, inspections of foreign sites are usually

106. *Id.*

107. *Id.*

108. OIG, CHALLENGES, *supra* note 2, at 39.

109. *Id.* at 16.

110. *Id.* at 21.

111. *Id.*

conducted after a clinical trial is already completed. Conducting inspections in this manner is not the most effective strategy to get sponsors and investigators to comply with regulations, and, by then, it is too late to correct possible data or ethics problems.¹¹² However, increasing inspections of foreign clinical trials while they are actually ongoing would prove to be far more effective of an enforcement strategy. Targeting clinical trials in countries not previously inspected or where GCP standards are novel could be more effective if the FDA used registration data submitted to the Agency either before or concurrent to the beginning of a trial to specifically pursue ongoing high risk clinical trial sites. The Agency already conducts inspections of domestic early-phase clinical trials on a targeted basis, thus the FDA could target ongoing early-phase foreign trials for inspection as well.¹¹³ By specifically targeting ongoing high-risk foreign trials, the FDA would maximize its limited resources.

The FDA may not be able to obtain data on these ongoing foreign clinical trials if an applicable rule is not possible under statute, or if legislation fails. The FDA may also be reticent to expand its registration requirements in consideration of the sovereignty of other countries and the role of foreign regulatory authorities.¹¹⁴ In addition, FDA inspections of foreign clinical trial sites may duplicate efforts of other regulatory bodies, unduly burdening sponsors and investigators in complying with separate findings.¹¹⁵ If this is the case, the FDA will need to rely on international cooperation and agreements with foreign regulatory bodies to effectively monitor ongoing foreign clinical trials.

A. Regulation through the Alien Tort Statute

If the regulatory gaps had been filled and recommendations of the OIG had been addressed back in 1996, would the harm have been prevented or minimized for the children participating in the Kano clinical trials? One would hope that the primary goal of current foreign clinical trial regulation would be to prevent a tragedy like the one in Nigeria from occurring again. Although the child victims of Kano did not receive the benefit of adequate public health protections, they did eventually get some reprieve in federal court.

The Alien Tort Statute (ATS) has provided a means for foreign nationals to bring tort actions committed in violation of the law of nations under the jurisdiction of the federal district courts.¹¹⁶ In *Abdullahi v. Pfizer, Inc.*, the

112. *Id.* at 36.

113. *Id.* at 39.

114. OIG, CHALLENGES, *supra* note 2, at 39.

115. *Id.* at 40.

116. Alien Tort Statute, 28 U.S.C.A. § 1350 (West 2011).

Second Circuit held that the child victims of the Trovan debacle and their guardians had a cause of action under the ATS for a violation of the norm of customary international law prohibiting the medical experimentation on human subjects without their consent (i.e. a violation of informed consent).¹¹⁷ Subsequently, the Supreme Court refused to hear Pfizer's petition for certiorari.¹¹⁸ Shortly after, Pfizer announced it had settled all outstanding lawsuits involving accusations that it tested Trovan on the children in Nigeria without receiving adequate informed consent.¹¹⁹ This regulation through tort seems to provide a viable forum for clinical trial subjects whose informed consent rights have been violated.

However, this restitution occurs after the fact of injury. An effective regulatory scheme should prevent these incidents from occurring in the first place.

In addition, it is unclear whether future victims could bring an action under the ATS against corporate defendants. In *Kiobel v. Royal Dutch Petroleum Co.*, the Second Circuit indicated that the ATS does not confer jurisdiction for a cause of action against corporations.¹²⁰ The Second Circuit's *Kiobel* decision presents a major roadblock to causes of action which are similar to the one brought by plaintiffs in *Abdullahi*. According to the *Kiobel* ruling, if a plaintiff brings a cause of action for a violation of informed consent under the ATS against a corporate defendant like Pfizer, the complaint may be dismissed merely because ATS does not confer jurisdiction against such defendants. It is likely that the Supreme Court will soon have to decide on this apparent inconsistency, but until then, holding pharmaceutical sponsors liable for violations of informed consent will be an uncertain option for aggrieved clinical trial subjects. While the potential for tort litigation in a federal district court may act as a deterrent to violative conduct, a globalized regulatory system focused on preventative public health monitoring and regulation is a more viable and effective option.

III. TOWARDS A GLOBALIZED REGULATORY SCHEME

The ICH-GCP guidelines provide a good framework for standardization

117. *Abduhalli v. Pfizer, Inc.*, 562 F.3d 163, 187 (2d Cir. 2009) (holding that Nigerian children and their guardians alleging a violation of the prohibition on nonconsensual medical experimentation had standing under the Alien Tort Statute).

118. *Pfizer, Inc., v. Abdullahi*, 562 F.3d 163 (2d Cir. 2009), *cert. denied*, 130 S.Ct. 3541 (2010).

119. Bill Berkrot, *Pfizer settles remaining Nigeria, US Trovan suits*, REUTERS (February 22, 2011, 6:18 PM), <http://af.reuters.com/article/investingNews/idAFJJOE71L0MV20110222>.

120. *Kiobel v. Royal Dutch Petrol. Co.*, 621 F.3d 111, 145 (2d Cir. 2010) (holding ATS confers jurisdiction only over claims against individuals, not corporate entities; thus the corporate defendant was not subject to liability under the ATS).

and ethical oversight of clinical trials globally. The FDA and European Medicines Agency (EMA) are currently collaborating on inspections through their GCP Initiative, designed to identify areas of harmonization, share, and effectively utilize resources for joint inspections.¹²¹ Continuing harmonization efforts and joint inspections with EMA are positive steps toward implementing best practices for conducting inspections, reducing duplicative inspections, and fostering understanding and collaboration between international regulatory agencies.¹²² The Initiative could set the tone and provide groundwork for other regulatory authorities, especially in those of developing or emerging countries, for the acceptance and adherence to harmonized global standards for conducting clinical trials. To further the goal of harmonization and global adherence to GCP, the FDA engages in outreach and capacity building throughout the world.¹²³ The goal of the FDA outreach is not only to ensure that foreign countries develop an understanding of the clinical trial oversight process and to incorporate GCP into their regulatory processes, but also to provide training and expertise to these countries.¹²⁴

Another example of multinational collaboration is the Pan American Network for Drug Regulatory Harmonization (PANDRH), which provides a forum for the FDA to work with all countries in the Americas to focus on harmonization of drug regulation.¹²⁵ Additionally, the FDA recently established permanent international presence in Latin America, Europe, the Middle East, Africa, India, and China to leverage the activities and resources of trusted regulatory foreign counterpart regulatory authorities.¹²⁶ Hopefully the FDA furthers these efforts to areas of the globe where regulatory authorities are not as “trusted” and clinical trial oversight is not yet as developed. FDA should also continue to develop inspectional agreements, especially with the emerging BRIC and developing countries to further the goals of ensuring data quality and human subject protection.¹²⁷

While harmonization, collaboration, and joint inspections are particularly important to effective and ethical oversight of clinical trials, the FDA should still pursue efforts to acquire standardized data from ongoing foreign

121. OIG, CHALLENGES, *supra* note 2, at 40 (noting that the EMA is an agency of the European Union, located in London, and is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union).

122. *Id.*

123. *Id.* at 6-7.

124. *Id.* at 7.

125. *Id.*

126. *International Programs: FDA Globalization*, U.S. FOOD AND DRUG ADMINISTRATION, <http://www.fda.gov/InternationalPrograms/FDABeyondOurBorders/ForeignOffices/default.htm> (last updated July 21, 2011).

127. BRIC countries include Brazil, Russia, India, and China.

clinical trials that will be used to support U.S. marketing applications. International data sharing agreements could help solve the problem concerning the lack of information on ongoing foreign clinical trials. The FDA could create multilateral data-sharing agreements with other countries, including data for Phase I trials. Access to an international trial registry would also help close the data gap. The FDA and other regulatory bodies could link into clinical trial registries and exchange information.

The World Health Organization (WHO) currently maintains the International Clinical Trials Registry Platform (ICTRP) as means to access trial registration data sets provided by international clinical trial registries, including ClinincalTrial.gov.¹²⁸ The ICTRP could feasibly serve as a means for more robust data sharing. The FDA could link into the ICTRP for complete standardized data when the Agency needs to obtain information on foreign clinical trials not conducted under an IND. The FDA would be able to utilize the ICTRP as a public health surveillance tool for clinical trials. Data monitoring and statistical analysis could be done through access to the trial registration data sets. When inconsistencies and unusual patterns in the data are found, WHO registry network member countries could be alerted to concerns related to the identified clinical trials.¹²⁹ Countries that insist on not bringing their regulatory schemes up to acceptable international standards and refuse to participate in an international data sharing agreement could be listed publicly on the WHO ICTRP website. This sort of “black list” would provide some incentives for these countries to catch up to acceptable standards. The list may also scare pharmaceutical companies away from sponsoring trials in these countries. Sponsors may bring more scrutiny upon themselves from the FDA when they submit information indicating their trials were conducted in these pariah countries. Overall, international data sharing and an international clinical trial registry are pragmatic solutions to the FDA’s limitations to sufficient foreign clinical trial oversight.

The emergence and utilization of foreign clinical trials to support U.S. marketing applications have presented the FDA with significant issues regarding its oversight of these clinical trials, specifically its limited

128. The ICTRP is a global initiative that aims to make information about all clinical trials involving humans publicly available. It aims to improve the comprehensiveness, completeness and accuracy of registered clinical trial data, to communicate and raise awareness of the need to register clinical trials, to ensure the accessibility of registered data, to build capacity for clinical trial registration, to encourage the utilization of registered data, and to ensure the sustainability of the ICTRP. See *Welcome to the WHO ICTRP*, WORLD HEALTH ORGANIZATION, <http://www.who.int/ictrp/en/> (last visited, Jan. 11, 2012).

129. The WHO Registry Network provides prospective trial registries with a forum to exchange information and work together to establish best practice for clinical trial registration. See *The WHO Registry Network*, WORLD HEALTH ORGANIZATION, <http://www.who.int/ictrp/network/en/> last visited, Jan 11,2012).

awareness of ongoing foreign trials, the ability to obtain complete and quality data, and to ensure the ethical treatment of human research subjects. In order to protect the public health by assuring the safety and efficacy of drugs and biologics, the FDA must progressively adapt its regulation of foreign clinical trials to keep pace with globalization. Ultimately, if FDA oversight of foreign clinical trials is to improve the agency must first address limitations of the data that is submitted from sponsors and clinical investigators. The FDA should require more robust and standardized electronic clinical trial data and continue to build upon its clinical trials registry and internal database. With more complete data, the FDA will be able to perform analyses and monitor trends to determine where problems exist and more effectively target inspections. To effectively monitor foreign clinical trials, the FDA will have to become aware of any and all foreign clinical trials that sponsors will utilize for U.S. marketing applications before the trials begin or while they are still ongoing. Thus, to tackle concerns with the conduct of foreign clinical trials the Agency will have to expand its regulatory oversight over these trials. If the FDA cannot do this through its administrative authority or through new legislation, it will have to look increasingly towards the international community for cooperation and further harmonization.