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Clinical Trials in Developing Countries

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Introduction

The global pharmaceutical industry is a trillion dollar business.² The foundation of the pharmaceutical industry is built on developing new drugs for regulatory approval to be sold to people all over the world.³ The United States is the largest pharmaceutical market in the world and companies rely on having new products approved for sale in the United States.⁴ The last decade in the United States saw the number of newly approved drugs by the Federal Drug Administration (“FDA”) decline and fail to keep pace with the increase in the amount of money spent to research and develop new drugs.⁵ The result has been research and development spending becoming an area where pharmaceutical companies are increasingly looking to lower

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² *IMS Health Study Forecasts Global Spending on Medicines to Reach \$1 Trillion Threshold in 2014, Driven by Greater Access*, IMSHEALTH (Nov. 19, 2013), <http://www.imshealth.com/portal/site/imshealth/menuitem.c76283e8bf81e98f53c753c71ad8c22a/?vgnextoid=96bdd595ae072410VgnVCM10000076192ca2RCRD>.

³ *Id.*, (“Growth Expected to Accelerate from Low Point in 2013 To 5-7 Percent in 2017; Rising Number of Innovative New Drugs Expected To be Approved Over Next Five Years ”)

⁴ *See* Top Line Market Data, Press Room, IMSHEALTH (Mar. 19, 2013)

http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/2012_U.S/Channel_Distribution_by_Non-Discounted_Spending_U.S.pdf (United States pharmaceutical market in 2012 was \$325.8 Billion); *see* Top Line Market Data, Press Room, IMSHEALTH (June 2013), http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/Total_World_Pharma_Market_Toplevel_metrics_2012-17_regions.pdf, (the United States and Canada combined in 2012 was the largest region in the world at \$348.7, next largest region was Europe at \$221.8 Billion).

⁵ *See Evolution or revolution? McKinsey perspectives on drug and device R&D*, (August 2012), available at

http://www.mckinsey.com/insights/health_systems_and_services/restoring_value_to_biopharmaceutical_r_and_d; *See also* AJAY DHANKHAR ET AL., *Escaping the sword of Damocles: Toward a New Future for Pharmaceutical R&D*, (August 2012), (“Restoring value to biopharmaceutical R&D: After years of seeing value destroyed by R&D excesses, biopharmaceutical companies can gain healthier returns—but only if they recognize several new imperatives”).

their costs.⁶ The low return on investments, the lack of available research subjects and the high costs of clinical trials has led companies to conduct a majority of clinical trials outside of the United States, including in developing countries.⁷

With more clinical trials occurring outside the United States, and the United States accounting for more than a third of the total pharmaceutical market, public concern in the United States has increased.⁸ The concern is two-fold. The first concern is the increased vulnerability for human research subjects in clinical trials located in developing countries where regulatory enforcement is weak.⁹ The second concern is how the weak regulatory systems at the trial location increases the potential for a product reaching the market based on invalid clinical trial data.¹⁰

⁶ Dhankar, *supra* note 5, at 5; *See also* Gardiner Harris, *F.D.A. Officials, Hoping to Stave Off Critics, Point to Increased Drug Approvals*, N.Y. TIMES, November 3, 2011, at A18, (“increase in drug approvals is good news for the pharmaceutical and biotechnology industries, which have failed to produce many new drugs in recent years. New drug approvals peaked in the mid-1990s and have generally declined since then despite increases in research spending. Major drug makers have steadily cut their research spending since 2008 because of poor productivity.”).

⁷ Dep’t of Health & Human Serv., OEI-01-08-00510, *Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials*, 2 (June 2010), [hereinafter 2010 HHS OIG Report].

⁸ *See* Donald L. Bartlett & James B. Steele, *Deadly Medicine*, VANITY FAIR, (Jan. 2011), <http://www.vanityfair.com/politics/features/2011/01/deadly-medicine-201101> (discussing if the number of people killed by prescriptions drugs in the United States will increase because of the weak regulation at clinical trial locations in developing countries); *See also*, 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/>, (discussing the appeal of holding clinical trials in developing countries and the ethical issues raised by this research trend); *See generally* *The Body Hunters*, WASHINGTON POST, <http://www.washingtonpost.com/wp-dyn/world/issues/bodyhunters/> (last visited March, 28, 2014) (“In this six-part series, the Post examines the booming, poorly- regulated system of international clinical drug testing that far too often preys on the poor and uneducated and betrays its promises to patients and consumers.”).

⁹ *See supra* note 8 and accompanying text.

¹⁰ *See supra* note 8 and accompanying text.

The FDA requires clinical trials conducted outside of the United States to be conducted in accordance with Good Clinical Practice (GCP) and adhere to the local regulations.¹¹ Local regulatory agencies in developing countries similarly require GCP be followed.¹² Despite the proliferation in regulation from the FDA and in developing countries, the current approach leaves clinical trial participants in developing countries vulnerable to abuse and opens up individuals to harm around the world that take a pharmaceutical drug that was approved based on invalid data.¹³ The main problem in clinical trial research in developing countries is the inability of the FDA to provide adequate oversight and the reliance on local regulatory agencies to enforce the law.¹⁴

This paper argues that a three-prong approach involving the enforcement of existing FDA regulations, the creation of international partnerships between regulatory bodies, and the development of private peer-to-peer partnerships between pharmaceutical companies can work together to prevent harm to research subjects in the developing world and stop harmful drugs from being approved based on invalid clinical trials. Each stakeholder can work together using

¹¹ 21 C.F.R. § 312.120 (2013), (“For the purposes of this section, GCP is defined 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. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study...and (ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.”).

¹² Daniel Liu, *Good Clinical Practice-Compliant Clinical Studies in China*, PHARMAFOCUSASIA http://www.pharmafocusasia.com/research_development/good-clinical-practice-Compliant-Clinical-Studies-China.htm (last visited May 7, 2014); The Drugs and Cosmetics Rules, 1945 (as amended up to the June 30th, 2005) [hereinafter Drug and Cosmetics], *available at* <http://cdsco.nic.in/html/Drugs&CosmeticAct.pdf>.

¹³ See *supra* note 8 and accompanying text.

¹⁴ Gardiner Harris, *Concern Over Foreign Trials for Drugs Sold in U.S.*, N.Y. TIMES, June 22, 2010, at A14.

past safety and ethical issues involving clinical trial research on human subjects, to prevent a reoccurrence of past behavior.¹⁵

Part one of this paper provides an overview of the clinical trial process, the market forces that have shifted the geographical footprint of clinical trials, where the clinical trial market is going and the current FDA regulation of domestic clinical trials, data from clinical trials conducted in developing countries. Part two looks at international regulations and the rise of clinical trials in China and India to illustrate international regulation of clinical trials in developing countries, the opaque information surrounding clinical trials in developing countries, its impact on the FDA and United States market.¹⁶ Part three proposes a three-prong solution to address the ethical and safety questions for the stakeholders involved.

I. The Clinical Trial Market

A. Clinical Trials in The United States

The development of a new drug for approval in the United States by the FDA requires the submission of clinical trial data displaying the efficacy and safety of the new drug.¹⁷ This is the end point of the clinical trial process. To get to this point a company has to navigate a process

¹⁵ *How Tuskegee Changed Research Practice*, CDC <http://www.cdc.gov/tuskegee/after.htm> (last updated Sept. 24, 2013).

¹⁶ To properly illustrate and analyze the problem of ethical research of human subjects in developing countries and the effect on product users around the globe I selected countries that have seen tremendous growth in their clinical trial market, have increased regulation as result of the growth, and what the effect has been on research subjects and product users.

¹⁷ 21 C.F.R. § 314.50 (2013) (“A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.”).

that is lengthy, heavily regulated, and is dependent on the availability of research subjects who are willing to participate in the clinical trial process.¹⁸

The clinical process begins with clinical testing on animals and then submission of an investigational new drug (IND) application to the FDA.¹⁹ The IND contains information for the proposed human testing from the sponsor of the clinical trial.²⁰ The IND is then reviewed by the FDA for approval.²¹ Institutional Review Boards (IRB) play the part of making sure that the proposed study is acceptable based on the clinical trial protocols proposed by the sponsor, the protection of research subjects and the information available to potential research subjects.²²

Following IND approval, phase I trials can begin. Phase I trials are conducted on twenty to eighty healthy research subjects and are designed to determine the side effects, and the rate in which the drug is metabolized and excreted.²³ Phase II trials focus on research subjects who suffer from the ailment that the drug is designed to target and usually contain research subjects numbering in the double digits to three hundred.²⁴ If phase II trials indicate that the drug is effective, phase III trials can begin.²⁵ Phase III trials focus on the safety and efficacy of the drug across various populations, different dosage levels, and how the drug interacts with other medications.²⁶ Phase III trials can include research subjects that number in the thousands.²⁷

¹⁸ See Joseph A. DiMasi, et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003).

¹⁹ 21 C.F.R. § 312 (2013); see also *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last updated Apr. 25, 2014) (provides a simplified overview of the drug review process).

²⁰ See *supra* note 19 and accompanying text.

²¹ *Id.*

²² *Id.*

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ *Id.*

The next step is for the sponsor to submit a new drug application (NDA) to the FDA that contains the information from the clinical trial results and relevant analyses.²⁸ At this point the FDA can reject, approve or request further information based on the NDA submitted.²⁹ With the average cost of bringing a new drug to market estimated to be between \$800 million and in excess of five billion dollars, the decisions made during the clinical process have huge financial impact.³⁰ The time period from preclinical testing to approval is estimated to take ten to fifteen years on average.³¹ At the completion of each phase the decision must be made on whether to move the product to the next phase or to abandon the research. The R&D costs increase as a product moves along the drug discovery process.³² The prospect of failure also increases at each phase of the drug discovery process.³³ Successful trials are abandoned if the product being tested is not projected to cover its research costs and provide a return for the company.³⁴

IND applications are not required for clinical trials that are conducted entirely outside the United States.³⁵ Further, sponsors can submit a NDA based solely on clinical trial data from outside the United States that was never subjected to an IND approval.³⁶ Only after the trials are

²⁷ *Id.*

²⁸ See *supra* note 17 and accompanying text.

²⁹ See *supra* note 19 and accompanying text.

³⁰ DiMasi, *supra* note 18 at 173; Matthew Harper, *The Cost Of Creating A New Drug Now \$5 Billion, Pushing Big Pharma To Change*, FORBES (Aug. 11, 2013, 11:10AM), <http://www.forbes.com/sites/matthewharper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/>.

³¹ Pharmaceutical Research and Manufacturers of America, *2013 Biopharmaceutical Research Industry Profile*, (July 2013), <http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf>.

³² Fabio Pammolli, et al., *The productivity crisis in pharmaceutical R&D*, NATURE (June 2011), http://www.nature.com/nrd/journal/v10/n6/fig_tab/nrd3405_F1.html.

³³ *Id.* at figure 2 (showing the increase in attrition rates at each phase).

³⁴ Harper, *supra* note 30 (quoting Roger Perlmutter, head of Merck R&D, saying, “One common mistake is allowing projects to linger on when the odds of success have become low”).

³⁵ 21 C.F.R. 312.120 (2013); OIG FOREIGN CLINICAL TRIALS REPORT *supra* note 7, at 2;

³⁶ 21 C.F.R. § 312.120 (2013); 21 C.F.R. § 314.106 (2013).

concluded does the FDA require that sponsors submit information that the study was conducted in line with GCP showing the qualifications of the clinical investigators, review of the trial by an independent committee and summary of adherence to the ethical protocols.³⁷ The relationship between foreign regulatory authorities and the FDA is often unbalanced.³⁸ In developing countries the disparity is even greater.³⁹ This is perhaps the most unique problem facing the FDA as they increasingly rely on regulatory bodies outside the United States and in developing countries.

B. Clinical Trial Regulation in The United States and The Acceptance of Foreign Data

The protection of research subjects participating in clinical trials in the United States began with the passing of the National Research Act in 1974 establishing the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research.⁴⁰ Five years later the Belmont Report was released and endorsed by the United States as the regulation of research of human subjects.⁴¹ The Belmont Report builds on the Nuremburg Code and the Helsinki declaration.⁴² Regulations were developed in the United States to govern the approval process involving the use of clinical trial data from outside the United States.⁴³ For domestic clinical trials, following the approval of the IND, human subjects must have provided legally effective informed consent and the trial must be conducted in accordance with GCP.⁴⁴

³⁷ 21 C.F.R. § 312.120 (2013).

³⁸ OIG FOREIGN CLINICAL TRIALS REPORT *supra* note 7, at p 2.

³⁹ *Id.*

⁴⁰ *See supra* note 15.

⁴¹ Office of Human Subjects Research, Nat'l Insts. of Health, *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>.

⁴² *Id.*

⁴³ 21 C.F.R. § 314 (2013); 21 C.F.R. § 312.120 (2013).

⁴⁴ 21 C.F.R. § 50.20 (2013); *see supra* note 11 and accompanying text.

The FDA regulation of the use of foreign clinical data in submissions for drugs to be approved in the United States is similar to the regulations for domestic trials. One difference, as noted above in section A, is the acceptance of clinical data not conducted under an IND.⁴⁵ Instead the FDA requires that the NDA submission include information showing that the clinical trial was conducted under the local equivalent to IND.⁴⁶ The regulations require foreign clinical trials, “be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee and informed consent from subjects.”⁴⁷ In addition the clinical data submitted by the sponsor must show that it is applicable to the US population, that the clinical trials were performed by clinical investigators with recognized competence, and the data can be considered valid without an onsite inspection by the FDA, or if the FDA wants to it can validate the data through an on site inspection or other means.⁴⁸

As companies sought to increase their return on R&D investment by conducting clinical trials in developing countries, the safety and ethics problems that confronted clinical trial research in the developed countries did not go away, rather they followed sponsors to the developing countries that provide fertile ground for clinical trial research.⁴⁹

C. The Globalization of Clinical Trials

⁴⁵ 21 C.F.R. § 312.120 (2013).

⁴⁶ U.S. DEP’T OF HEALTH & HUMAN SERV., GUIDANCE FOR INDUSTRY AND FDA STAFF: FDA ACCEPTANCE OF FOREIGN CLINICAL STUDIES NOT CONDUCTED UNDER AN IND FREQUENTLY ASKED QUESTIONS (Mar. 2012), [hereinafter 2012 FDA Guidance], *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>.

⁴⁷ *Id.*

⁴⁸ *Id.* at p 1.; 21 C.F.R. § 312.120 (2013).

⁴⁹ *See supra* note 8 and accompanying texts; *see also* Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816 (2009).

In the 1990's research and development costs soared while the number of newly approved drugs remained stagnant.⁵⁰ To improve their financial situation pharmaceutical companies began to look for ways to redesign their approach to R&D.⁵¹ Soon, pharmaceutical companies began to outsource aspects of the clinical process to third parties, with the goal of lowering costs and increasing enrollment of human subjects by running clinical trials across the globe.⁵²

The rise of outsourcing has been a direct benefit to Contract Research Organizations (CRO).⁵³ CROs have lowered costs for pharmaceutical companies and continued the movement of clinical trials to developing countries.⁵⁴ The FDA defines a CRO as a corporation that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor to design, select, monitor, evaluate, and/or prepare materials to be submitted to the FDA.⁵⁵ CROs' services can provide a range of R&D functions needed by their clients as internal departments have been cut due to downsizing.⁵⁶ Outsourcing during the drug development

⁵⁰ See *supra* note 6 and accompanying texts.

⁵¹ DHANKAR ET AL., *supra* note 5.

⁵² See, Miriam Shuchman, *Commercializing Clinical Trials--Risks and Benefits of the CRO Boom*, 357 N. ENG. J. MED. 1365, (Oct. 2007) (discussing the rise of contract research organizations (CROs) due their ability to provide speed and efficiency in conducting clinical trials).

⁵³ *Id.* at 1366 (highlighting the growth in the CRO market from \$7 billion in 2001 to \$17.8 billion in 2007); see also Ed Silverman, *Why Contract Research Organizations Are So Hot*, FORBES (Oct. 4, 2011, 7:31PM), <http://www.forbes.com/sites/edsilverman/2011/10/04/why-contract-research-organizations-are-so-hot/>.

⁵⁴ Shuchman *supra* note 53 and accompanying texts.

⁵⁵ 21 C.F.R. § 312.2(b) (2013).

⁵⁶ Kenneth Getz et al., *Resizing the Global Contract R&D Services Market A new study revises estimates of the market*, CONTRACTPHARMA (May 30, 2012), http://www.contractpharma.com/issues/2012-06/view_features/resizing-the-global-contract-rd-services-market/#sthash.j3CZyPyx.dpuf.

process has led to the CRO market to almost triple in size from \$7 billion in 2001, to an estimated 2014 size of \$23.6 billion.⁵⁷

Because CROs have been able to conduct efficient, fast paced trials for their partners, they have largely replaced the academic institutions that were the traditional partners of pharmaceutical companies in drug development.⁵⁸ The participation of CROs and their effect on clinical trial research has been lauded in the industry research world and criticized elsewhere.⁵⁹ CRO's have been questioned as contributing to research abuse in clinical trials in the United States, Canada, and Britain.⁶⁰ At the same time CROs have been accused of also hindering research as a result of over zealous enforcement of regulations.⁶¹

⁵⁷ Shuchman *supra* note 53 and accompanying text; *ISR Projects the 2014 CRO Market to Be Worth \$23.6 Billion*, FIERCECRO (Feb. 10, 2014). <http://www.fiercecro.com/press-releases/isr-projects-2014-cro-market-be-worth-236-billion-read-more-httpwwwdigitalj>.

⁵⁸ Shuchman *Supra* note 53, at 1366.

⁵⁹ See Shuchman *supra* note 52 (acknowledging that CRO's offer greater spend and efficiency while questioning CRO reporting methods and commenting on the industry's tendency to internalize problems); *but see*, Lutz Heinemann & Marcus Hompesch, *Role of Physicians in the Pharmaceutical Industry and Clinical Research Organizations: Take More Pride in Your Work*, 2 *Diabetes Sci Technol.* 4, 707-709, Jul 2008, available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769751>, (arguing Dr. Shuchman focused on CRO related negative events while ignoring similar events in academia).

⁶⁰ See Shuchman *supra* note 52, at 1368 (“SFBC International was cited by a Bloomberg report as having inadequate oversight of a clinical trial location in Florida which led to SFBC settling a shareholder class action lawsuit for \$28.5 million...SFBC clinical trial in Montreal included a patient with tuberculosis who remained in the trial and nine other trial participants eventually tested positive for tuberculosis...CRO Parexel managed a clinical trial in Britain where subjects taking the drug had organ failure and British regulatory agency found that the Parexel physician involved in the study had inadequate training and Parexel had no formal system in place for providing round-the-clock medical coverage.”); *see also* Elisabeth Rosenthal, *When drug trials go horribly wrong*, N.Y.TIMES, Apr. 7, 2006, available at <http://www.nytimes.com/2006/04/07/world/europe/07iht-drug.html?pagewanted=all>.

⁶¹ See Trudie Lang & Sisira Siribaddana, *Clinical Trials have Gone Global: Is this a good thing?*, PLOSMEDICINE (June 2012), <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001228>, (discussing examples of “inappropriate clinical trial conduct that could be adversely impacted by...overly keen CROs...can unnecessarily overburden and increase the cost of clinical trials”).

The results of outsourcing in R&D and the globalization of clinical trials were soon realized in both developed and developing countries. Clinical data from trials conducted outside of the United States is in over eighty percent of approved marketed drug applications by the FDA.⁶² Less than half of all clinical trials are conducted in the United States.⁶³ This is the combined result of research and development economic pressures, regulatory oversight of trials conducted in the United States and the lack of willing research subjects.⁶⁴ Two large recipients of the clinical trial migration are China and India.⁶⁵ Recently, China has seen their clinical trial market grow at a rate of 15%.⁶⁶ While India initially saw remarkable growth in their clinical trial market, recent safety and ethical concerns have derailed the industry and highlighted the risks for sponsors and research subjects in conducting clinical trials in emerging markets.⁶⁷ Still, the India clinical trial market was recently valued at \$450 million and is projected to increase in size to over \$1 billion.⁶⁸

⁶² 2010 HHS OIG Report, *supra* note 7, at p 10.

⁶³ *Id.*

⁶⁴ Kristen Brooks, *CRO Outlook & Market Trends: Innovation tied to globalization & collaboration*, CONTRACTPHARMA (June 5, 2013), http://www.contractpharma.com/issues/2013-06/view_features/cro-outlook-market-trends/; Gregory Lopes, *Drug Makers Look East For Testing*, WASH. TIMES, Dec. 8, 2007, (large populations in India and China provide a large pool for companies to gather clinical data at a faster pace).

⁶⁵ *Report: Clinical trials market growing rapidly*, CENTERWATCH (July, 5, 2011, 12:16PM), <http://www.centerwatch.com/news-online/article/1827/report-clinical-trials-market-growing-rapidly#sthash.nTQlzCSn.dpbs>.

⁶⁶ Rajesh Jain, *India's clinical trials industry—in detraction mode*, KPMG SECTOR INSIGHTS 25 (June 2012), <http://www.kpmg.com/IN/en/IssuesAndInsights/ArticlesPublications/kbuzz/Documents/Kbuzz-Issue-18.pdf>.

⁶⁷ *Id.*

⁶⁸ Dinsa Sachan, *Supreme court ruling brings clinical trials to a halt in India*, ROYAL SOCIETY OF CHEMISTRY, (Oct. 15, 2013) <http://www.rsc.org/chemistryworld/2013/10/supreme-court-ruling-clinical-trials-halt-india> (discussing the Frost & Sullivan research report that estimated that the India clinical trial industry was worth \$450 million (£282 million) in 2011).

The globalization of clinical trials has been beneficial to the pharmaceutical industry, as they have achieved the goal of lowering costs, increasing patient enrollment and avoided complex regulatory burdens.⁶⁹ This has coincided with industry investment in China and India as companies looked to increase their presence and view the countries as not only a low cost location, but also countries where drugs can be marketed and sold and thus lessen their reliance on developed markets.⁷⁰ However, both countries have suffered recent setbacks involving harm to research subjects and questions on the validity of data from their clinical trials that stem from their inadequate regulatory systems.⁷¹

This rise of clinical trials taking place outside the United States has presented unique challenges to the FDA.⁷² As the FDA is responsible for dealing with the problem of regulating the information that is obtained from clinical trials in developing countries to try to ensure the protection of the human subjects where the research is taking place and that the information obtained is valid when the data is submitted in a NDA, the need for increased international and domestic regulations in partnership has risen.⁷³

II. International Standards and Domestic Regulation of Clinical Trials

A. Nuremburg Code, Helsinki Declaration, Belmont Report and International Conference on Harmonization

⁶⁹ Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816, 817 (2009), (“A pharmaceutical executive reported that a first-rate academic medical center in India charges approximately \$1,500 to \$2,000 per case report, less than one tenth the cost at a second-tier center in the United States.”) (“An important force that is moving clinical trials to developing countries is the increasingly bureaucratic and expensive regulatory environment in many wealthy countries.”).

⁷⁰ Robert Cyran & George Hay, *China’s Allure in Drug Research*, N.Y.TIMES, December 7, 2011, at B2.

⁷¹ See *supra* notes 66 and 68 and their accompanying texts.; see also Katie Thomas, *Drug Research in China Falls Under a Cloud*, N.Y.TIMES, July 22, 2013, at A1.

⁷² 2010 HHS OIG Report *supra* note 7, at p 1.

⁷³ 21 CFR 314.106 (2013); See 2010 HHS OIG Report *supra* note 7, at p 21.

The International regulation of clinical trial research on human subjects began after World War II. The Nuremburg Code was created following the completion of the Nuremburg Trials that involved the prosecution of Nazi physicians for war crimes following the discovery of their experiments on human research subjects.⁷⁴ The ten principles from Nuremburg Code serve as a blueprint for the ethical treatment of research subjects around the globe by requiring that research participation by human subjects is voluntary and informed.⁷⁵

The Declaration of Helsinki was adopted by the World Medical Association in 1964, “as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.”⁷⁶ The Declaration has subsequently been reformed numerous times to reflect societal changes, with the latest revision occurring in 2013.⁷⁷ At its core the Declaration of Helsinki provides ethical principles for physicians and others involved in human subject research to consider when conducting research with human subjects.⁷⁸

Following the development of various regulations on clinical research across the globe, each different than the next, it became apparent that there was a need for harmonization between

⁷⁴ Evelyn Shuster, *Fifty Years Later: The Significance of the Nuremberg Code*, 337 NEW ENGL. J. MED. 1436, (Nov. 13, 1997) available at <http://www.nejm.org/doi/full/10.1056/NEJM199711133372006>.

⁷⁵ *The Nuremberg Code*, reprinted in *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10*, Vol. 2, 181-82 (Government Printing Office 1949) (“The Nuremberg Code provides, inter alia: (1) subjects of medical experimentation must provide voluntary, informed consent; (2) the experiment must yield socially useful results that would not have been obtainable by other means; (3) the experiment should be conducted to minimize risk to the subject; and (4) the experiment must be terminated if the researcher believes that it may cause harm to the subject.”) available at <http://www.hhs.gov/ohrp/archive/nurcode.html>.

⁷⁶ WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2013), <http://www.wma.net/en/30publications/10policies/b3/>.

⁷⁷ *Id.*

⁷⁸ Shuster *supra* note 74, at p. 1440.

the various regulations.⁷⁹ This led to the creation of the International Conference on Harmonization (ICH).⁸⁰ The ICH is a collaborative effort by regulatory authorities in the United States, Japan and European Union that designs and recommends shared procedures and regulations designed to safeguard the safety and efficacy of clinical research for new drugs.⁸¹ In 1997 the FDA endorsed the GCP guidelines developed by the ICH for clinical trial research on human subjects to be used as guidance to the FDA.⁸²

While the globalization of clinical trials is over three decades old, public knowledge of this shift began to make headlines in 2000 following a six part series published by the Washington Post highlighting the practice and the ethical compromises that were made.⁸³ The use of foreign clinical trials in developing countries has continued to make public headlines.⁸⁴ Despite regulations designed to govern the use of foreign data, prevent harm to research subjects,

⁷⁹ *The Need to Harmonise*, ICH <http://www.ich.org/about/history.html> (last visited Apr. 23, 2014) (discussing the formation of the ICH between Europe, Japan and the United States).

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² Compare 21 C.F.R. § 312.120 (2013) (describing GCP 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.”), with INT’L CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, ICH (June 10, 1996), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf (“1.24 Good Clinical Practice (GCP) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.”).

⁸³ *The Body Hunters*, WASHINGTON POST, <http://www.washingtonpost.com/wp-dyn/world/issues/bodyhunters/> (last visited March, 28, 2014) (“In this six-part series, the Post examines the booming, poorly- regulated system of international clinical drug testing that far too often preys on the poor and uneducated and betrays its promises to patients and consumers.”).

⁸⁴ See *supra* note 8 and accompanying texts.

and protect the public from unsafe drugs, the FDA was roundly criticized for its response to the shifting locales of clinical trials and inability to monitor and inspect foreign clinical trials.⁸⁵

The Nuremberg Code, The Helsinki Declaration, The Belmont Report, The FDA, The EMEA and numerous other international agreements and regulatory bodies have all been in effect during the past two decades.⁸⁶ Nevertheless, clinical trials in China and India continue to present risk of harm to human research subjects and the prospect of invalid data due to the weak regulatory enforcement.⁸⁷ Subsequently the pharmaceutical industry has found itself in numerous legal and ethical quandaries resulting from clinical trials where instances of abuse to research subjects and invalid data continue to occur in part because of the major failing in developing countries to enforce regulations.⁸⁸

B. Clinical Trial Regulation in China

For the past quarter century China has been the economic medicine for the global economy.⁸⁹ This has been particularly true for the pharmaceutical industry.⁹⁰ Since 2006 China has grown from the ninth largest pharmaceutical market in world with sales of \$27 billion, to

⁸⁵ 2010 HHS OIG Report *supra* note 7; Harris *supra* note 14.

⁸⁶ Shuster *supra* note 74.

⁸⁷ Katie Thomas, *Drug Research in China Falls Under a Cloud*, N.Y.TIMES, July 22, 2013, at A1.; Benjamin Shobert, *Three Ways To Understand GSK's China Scandal*, FORBES (Sep. 4, 2013, 10:00AM)

<http://www.forbes.com/sites/benjaminshobert/2013/09/04/three-ways-to-understand-gsks-china-scandal/>; *see supra* notes 66 and 68.

⁸⁸ *Id.*

⁸⁹ *See Western firms have piled into emerging markets in the past 20 years. Now comes the reckoning*, THE ECONOMIST, (Mar. 8, 2014) available at

<http://www.economist.com/news/business/21598642-western-firms-have-piled-emerging-markets-past-20-years-now-comes>.

⁹⁰ Benjamin Shobert, *Pharma's Wild Ride in China*, FORBES (Jan. 6, 2014, 10:00AM)

<http://www.forbes.com/sites/benjaminshobert/2014/01/06/pharmas-wild-ride-in-china/> (discussing the expectations versus results of pharmaceutical companies active in China)

currently the third largest pharmaceutical market in the world with sales over \$70 billion.⁹¹ China has also proven to be fertile ground for clinical trial research recruiting due to the size of its population and the low cost of labor.⁹² An additional issue that is related to the growth of clinical trials but not a driver, is that in order for a new product to gain regulatory approval in China, the product's clinical trials must have taken place in China.⁹³ Thus a company looking to gain market access in China must conduct clinical trial research in China first. This usually is in the form of partnering with a Chinese company. These factors led to the growth in clinical trials in China of 47%.⁹⁴ By comparison the number of clinical trials conducted in the United States during the same period has decreased by an average of 6.5% annually.⁹⁵

In accordance with the market growth, China has developed and instituted numerous regulations on clinical research that are inline with adopted international regulations.⁹⁶ The China Food and Drug Administration (CFDA) is the equivalent of the FDA in China. The

⁹¹ Franck Le Deu ET AL., *Health care in China: Entering 'uncharted waters' Multinationals are flocking to take advantage of the opportunities, but long-term success is by no means assured.*, MCKINSEY, (Nov. 2012)

http://www.mckinsey.com/insights/health_systems_and_services/health_care_in_china_entering_uncharted_waters.

⁹² *The next phase: Opportunities in China's pharmaceuticals market* at 17, DELOITTE (2011) http://www.deloitte.com/view/en_CN/cn/ind/lshc/723313bbb0943310VgnVCM3000001c56f00aRCRD.htm#; Karen Politis Virk, *China's Clinical Trial Boom*, PHARMAFOCUSASIA (2011) http://www.pharmafocusasia.com/clinical_trials/chinas-clinical-trial-boom.htm (discussing how the China's population of over a billion people helps with patient enrollment and labor costs 60 to 80 percent less in China than in developed countries).

⁹³ *Id.*

⁹⁴ Gordon H. Sun et al., *The Calculus of National Medical Research Policy — The United States versus Asia*, 367 NEW ENGL. J. MED. 687, at 690 (Aug. 23, 2012), available at <http://www.nejm.org/doi/pdf/10.1056/NEJMp1206643>.

⁹⁵ *Id.*

⁹⁶ Wolfgang Hennig, *Bioethics in China: Although national guidelines are in place, their implementation remains difficult*, THE EUROPEAN MOLECULAR BIOLOGY ORGANIZATION, (Sep. 2006), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1559670>.

CFDA governs clinical trial research.⁹⁷ Chinese laws on clinical research refer to the Declaration of Helsinki as the foundation for research involving human subjects.⁹⁸ China requires that a research proposal be submitted to an ethical review committee where the proposal is either accepted or rejected.⁹⁹ The CFDA also requires that GCP be followed in line with international standards for human subject research.¹⁰⁰ One major difference between the ICH GCP guidelines and GCP in China is that the research subject is not required to sign the consent form, only the investigator.¹⁰¹ Another major difference is that the Chinese ethics regulations are not enforceable by law.¹⁰²

Thus despite the presence of regulation requiring independent ethical review boards, and other instruments to protect the research subjects and the trial outcomes, sponsors of clinical trials in China are rarely punished through these regulations. However, recently clinical trial outcomes in China have come under questioning based on accusations of fraud and bribery.¹⁰³

Misconduct was recently discovered by a GlaxoSmithKline internal audit. The report described a series of failures including the failure to report results from an animal study on a product that was now being tested in human research subjects, the failure to record research subject consent forms during clinical trials, the failure to track and document whether the approved clinical trial protocol was being followed, and contained allegations concerning

⁹⁷ *Id.* (“These regulations of biomedical research, clinical trials and clinical treatments are under the control of the State Drug Administration, and include instructions on protocol design, organization, conducting, monitoring, auditing, recording, analyzing and reporting.”).

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ Liu *supra* note 12.

¹⁰² Hennig *supra* note 96.

¹⁰³ *Supra* note 87 and accompanying text.

payments and kickbacks to the clinical investigators who were responsible for oversight of the trials.¹⁰⁴

Eventually GlaxoSmithKline fired their head of R&D in China over the clinical trial accusations and was accused of paying over \$490 million in bribes to increase sales.¹⁰⁵ Soon other allegations of corruption followed against other international pharmaceutical companies and the United States notified pharmaceutical companies that it was under investigation for violating the Foreign Corrupt Practices Act.¹⁰⁶ Skeptics point out that the Chinese investigation into the multinational pharmaceutical companies on bribery charges was in large part driven in an effort to lower drug prices and increase the standing of domestic pharmaceutical companies.¹⁰⁷ These fears exist despite the subsequent bribery charges against one of China's largest pharmaceutical distributors.¹⁰⁸ However other actions indicate that China may indeed be serious about rooting out corruption in their pharmaceutical industry.

An example that focuses on the validity of clinical trial data in China occurred involving a potential blockbuster for Bristol-Meyers Squibb.¹⁰⁹ The FDA delayed the drug Eliquis in 2012 after Bristol-Meyers discovered that the clinical trial records at a site in China were tampered

¹⁰⁴ Katie Thomas, *Drug Research in China Falls Under a Cloud*, N.Y.TIMES, July 22, 2013, at A1.

¹⁰⁵ John Carroll, *GlaxoSmithKline's research chief in China fired for data fraud*, FIERCEBIOTECH (June 11, 2013), <http://www.fiercebiotech.com/story/glaxosmithklines-research-chief-china-fired-data-fraud/2013-06-11#ixzz2xDn1Yf7m>.

¹⁰⁶ *Supra* notes 87 and accompanying texts.

¹⁰⁷ Benjamin Shobert, *Why Did One Of The World's Largest Generic Drug Makers Exit China?* FORBES (Feb. 3, 2014, 5:52PM), <http://www.forbes.com/sites/benjaminshobert/2014/02/03/why-did-one-of-the-worlds-largest-generic-drug-makers-exit-china/> (questioning the motives behind the recent increase in anti-corruption enforcement in China).

¹⁰⁸ *Id.*

¹⁰⁹ Drew Armstrong, *Chinese Trial Misconduct Delayed Bristol-Myers Medicine*, BLOOMBERG (July 9, 2013 12:01 AM), <http://www.bloomberg.com/news/2013-07-09/chinese-trial-misconduct-delayed-bristol-myers-medicine.html> (the drug eliquis is forecasted by analysts to reach over \$10 billion in sales annually).

with in order to hide GCP violations involving the wrong medication being dispensed to human research subjects.¹¹⁰ A Bristol-Meyers employee ahead of a FDA site inspection ordered a contract research employee from the contract research firm Pharmaceutical Product Development to change the research data to hide the GCP violation.¹¹¹ The contract research employee reported the cover-up to her supervisors.¹¹² Bristol-Meyers reported to the FDA that research subjects were given the wrong medicine, data was secretly changed, and serious adverse events were not reported.¹¹³ After the Bristol-Meyers reported the problems to the FDA, Bristol-Meyers and the FDA together removed the tampered clinical data, reanalyzed the valid clinical data and found the final positive result was not affected.¹¹⁴

China has solid regulations in place that are largely similar to those in the United States and European countries.¹¹⁵ The problem remains how to increase enforcement levels directed at maintaining ethical clinical research while not creating an atmosphere where companies feel that selective enforcement is taking place.

C. Clinical Trial Regulation in India

Like China, India has been a preferred location for sponsors of clinical trials.¹¹⁶ Conducting a clinical trial in India involves half the cost of running a trial in the United States and India's large population allows for easier patient recruiting.¹¹⁷ During the past decade India has been trying to catch up to the increase in clinical trials by amending and adopting

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.*

¹¹⁴ *Id.*

¹¹⁵ Henig *supra* note 96.

¹¹⁶ Madhur Singh *Should Clinical Trials Be Outsourced?*, TIME, (Aug. 07, 2008) <http://content.time.com/time/health/article/0,8599,1830334,00.html>.

¹¹⁷ *Id.*

regulations.¹¹⁸ Currently the regulation of clinical trials is the responsibility of the Central Drugs Standard Control Organization (CDSCO), through the Drug Controller General (DCG) which operates under Ministry of Health and Family Welfare (MoH and FW).¹¹⁹ Schedule Y of the Drugs and Cosmetic Act requires that a clinical trial sponsor in India must submit an application that is approved in writing by an Independent Ethics Committee and the DCG.¹²⁰ The CDSCO requires that the clinical trial be conducted in accordance with the approved protocol from the DCG and in compliance with GCP.¹²¹ Continuing problems with clinical trial regulation in India is that an audit certificate is not required and that previously the IECs were not required to be registered with the CDSCO.¹²²

Thus despite the regulations, violations continue to occur that show harm to research subjects that have resulted in death and the prospect of invalid trial data.¹²³ The growth in the Indian clinical trial market has stopped and declined following a series of discoveries involving the unethical treatment of research subjects and allegations of fraudulent data.¹²⁴ From 2008 to 2011 there were over a thousand deaths reported of research subjects enrolled in clinical trials.¹²⁵

¹¹⁸ Mohammed Imran et al., *Clinical research regulation in India-history, development, initiatives, challenges and controversies: Still long way to go*, JOURNAL OF PHARMACY & BIOALLIED SCIENCES, (Jan. 28, 2013), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3612334/#!po=63.3333>.

¹¹⁹ *Id.*

¹²⁰ *Id.*

¹²¹ *Id.*

¹²² Jain *supra* note 66, at p 26 (discussing how auditing certificates were only required if they were available compared to being mandatory in the EU and United States).

¹²³ *See supra* notes 66, 68 and accompanying text.

¹²⁴ *See supra* notes 66, 68 and accompanying text.

¹²⁵ Sue Lloyd-Roberts, *Have India's poor become human guinea pigs?*, BBC NEWSNIGHT, (October 31, 2012, 8:40PM), <http://www.bbc.com/news/magazine-20136654>; *but see* Narayanan Suresh, *India's clinical trial industry should look in the mirror*, BIOSPECTRUMASIA, (July 12, 2013), <http://www.biospectrumasia.com/biospectrum/opinion/191617/indias-clinical-trial-industry-look-mirror#.U2uX5q1dWWk>, (“in the eight years since 2005, more than 2,800 deaths of patients have occurred during clinical trials. Of these, only 89 or about three percent are

These discoveries have spurred the call for reform.¹²⁶ In July 2013 the National Institutes of Health (NIH), the United States medical research agency, suspended all ongoing NIH sponsored clinical trials in India as a result of the ongoing regulatory uncertainty.¹²⁷ The efforts culminated in October 2013 when the top Indian Court stopped ongoing clinical trials until the approval process was reviewed to see if protocol was followed when the clinical trials were approved.¹²⁸

III. Proposals For Improving Clinical Trial Regulation Enforcement

As illustrated above, the adoption of regulation in developing countries has not eliminated the concerns on the ethical research of human subjects and the ability to verify clinical trial data.¹²⁹ The risk of exploitation continues because of the inability at the local level to enforce regulations.¹³⁰ In this section I propose a three-prong approach to improve local regulation enforcement in order to prevent harm to research subjects and eliminate invalid clinical trials.

The three-prong solution involves enforcement of existing FDA regulations, international partnerships between regulatory bodies, and private peer to peer partnerships all with the focus of enhancing local enforcement in order to prevent harm to research subjects eliminate invalid data from clinical trial research.

attributable mainly due to the effects of the medical products under trial. Rest of the cases are due to terminal illnesses, advancing age, etc.”).

¹²⁶ Andrew Buncombe, *A heaven for clinical trials, a hell for India: Court orders government to regulate drugs testing by international pharmaceutical companies*, THE INDEPENDENT (Sep. 30, 2013), <http://www.independent.co.uk/news/world/asia/a-heaven-for-clinical-trials-a-hell-for-india-court-orders-government-to-regulate-drugs-testing-by-international-pharmaceutical-companies-8849461.html>.

¹²⁷ John Carroll, *NIH confirms it is shelving India drug trials in wake of new regs*, FIERCEBIOTECH (July 17, 2013), <http://www.fiercebiotech.com/story/nih-confirms-it-shelving-india-drug-trials-wake-new-regs/2013-07-17#ixzz2zkdwvmCU>.

¹²⁸ Sachan *supra* note 68 (“Clinical trials of NCEs are being conducted without following proper protocol, and companies are taking advantage of poor people.”).

¹²⁹ *See supra* notes 66, 68, 104, 105, 107, 126 and accompanying texts.

¹³⁰ *See supra* notes 66, 68, 104, 105, 107, 126 and accompanying texts.

A. FDA Enforcement of Existing Regulations

As discussed above in part one, the FDA has existing regulation governing foreign clinical data in submissions for drugs to be approved in the United States.¹³¹

In response to the globalization of clinical trials, the FDA responded with a large effort to increase its presence globally by opening up offices around the globe with the intent of assisting other regulatory agencies through joint-collaboration.¹³² The FDA issued guidance for how clinical trial sponsors and companies can comply with the requirements needed for acceptance of foreign clinical data in a NDA for studies both conducted under an IND and not conducted under and IND.¹³³ The guidance highlights that the enacted regulations require foreign clinical trials “be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee and informed consent from subjects.”¹³⁴

With the regulations already in place, the question turns to how to increase enforcement. Currently, the FDA is limited by its inability to mandate local regulatory agencies to enforce FDA regulations and this problem is heightened when neither the FDA nor the local agency is unaware that violations have occurred.¹³⁵ The lack of training and expertise is one of the main problems in developing countries.¹³⁶ Even where a regulatory system exists similar to the United States, like in India, the inability to provide adequate oversight exists because of lack of expertise and knowledge at the local levels.

¹³¹ See *supra* note 48.

¹³² *FDA Beyond Our Border*, FDA, (Dec. 9, 2008), <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm103044.pdf>.

¹³³ 2012 FDA GUIDANCE *supra* note 46.

¹³⁴ *Id.* at p 12.

¹³⁵ 2010 HHS OIG REPORT, *supra* note 7, at p 10.

¹³⁶ See *supra* note 8 and accompanying texts.

However, similar systems allow for sponsors to understand what is required and develop increased knowledge instead of having to spend time elsewhere that does not increase protection of clinical trials. The same is true for the FDA partnering with developing countries to train local regulatory workers and provide training for GCP. To correct this problem, the FDA can increase direct enforcement through the increase in their budget, and training local parties to assist in enforcement.¹³⁷ The increase in regulatory knowledge following training will allow for greater enforcement, as local parties begin to understand what is required and identify violations. In addition, the FDA can train clinical trial investigators from around the world in coordination with the risk based monitoring approach that was recently endorsed by the FDA for use by sponsors of clinical trials.¹³⁸

The risk-based monitoring approach is designed to prevent errors during clinical trials by focusing on monitoring activities that directly effect error prevention based on risk analyses.¹³⁹ The process of risk-based monitoring requires sponsors to, “identify critical data and processes...perform risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes, and then develop a monitoring plan that focuses on the important and likely risks to critical data and processes.”¹⁴⁰ To identify

¹³⁷ *Id.*

¹³⁸ U.S. DEP’T OF HEALTH & HUMAN SERV., GUIDANCE FOR INDUSTRY AND FDA STAFF: OVERSIGHT OF CLINICAL INVESTIGATIONS—A RISK-BASED APPROACH TO MONITORING, (August 2013) [hereinafter 2013 FDA GUIDANCE],

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>, (“Guidance is therefore intended to make it clear that risk-based monitoring, including the appropriate use of centralized monitoring...and reliance on technological advances (e.g., e-mail, webcasts, online training modules), can meet statutory and regulatory requirements under appropriate circumstances.”).

¹³⁹ *Id.* at p. 11, (“Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection and reporting of critical data and processes necessary for human subject protection and trial integrity.”).

¹⁴⁰ *Id.* at p. 11 (these include monitoring the obtainment of informed consent, and the site records and other).

the risks in a clinical trial includes looking to the geographic location of the trial and understanding the level of local clinical trial enforcement knowledge.¹⁴¹ The goal is to allow sponsors to develop dynamic clinical trial oversight based on the risks of each study.¹⁴²

The risk-based approach includes both centralized monitoring and on-site monitoring.¹⁴³ Centralized monitoring is the monitoring of a clinical trial by a sponsor at a location other than where the clinical trial is taking place.¹⁴⁴ Centralizing the monitoring process is viewed as a way to increase oversight through statistical analyses.¹⁴⁵ Centralized monitoring includes analyses of the need of on-site visits based on when the risk analyses identifies, “sites with data anomalies...high error rates, protocol violations, or dropouts relative to other sites”.¹⁴⁶ In sum the approach looks for outlier sites that can then be designated for a targeted on-site monitoring approach.¹⁴⁷

The risk-based approach will maximize the FDA’s resources by allowing for efficient regulation enforcement to protect human research subjects and clinical data by having sponsors focus on the high risk factors of clinical trials.¹⁴⁸ Also the risk-based approach avoids the cost and manpower questions that go with the call for increased FDA personnel in remote locations, while at the same time enforcing the existing regulations designed to protect human subjects and clinical data.¹⁴⁹ The FDA can also increase the uptake of the risk-based approach by leveraging

¹⁴¹ *Id.* at p. 11.

¹⁴² *Id.* at p. 2.

¹⁴³ *Id.* at p. 6, (discussing the strengths of both approaches and what to consider when electing a monitoring plan).

¹⁴⁴ *Id.* at p. 7.

¹⁴⁵ *Id.* at p. 5, (discussing a review of on-site monitoring that concluded more than 90% of the findings could have been found using centralized monitoring).

¹⁴⁶ *Id.* at p. 8

¹⁴⁷ *Id.* at p. 8

¹⁴⁸ *Id.* at p. 1.

¹⁴⁹ *Id.* at p. 1.

the locations where it does have an increased foreign presence and use its personnel and available money to spend on training local regulators.¹⁵⁰

To properly develop training partnerships and increase local regulator monitoring, there needs to be a strengthening of the regulatory partnerships between the FDA and other domestic regulatory groups.

B. Partnerships Between Domestic Regulatory Agencies

The FDA can use improved mechanisms to enforce existing regulations and achieve proper oversight of clinical trials by creating regulatory partnerships at the domestic and the international level. Regulatory partnerships between international countries first came out of the ICH in order provide industry guidance for conducting research with human subjects.¹⁵¹ More recently the FDA has entered into individual cooperating agreements with countries covering technology sharing, capacity building, technical cooperation in an effort to harmonize multilateral relations.¹⁵² These relationships can provide the knowledge and expertise sharing to make all parties stronger in the monitoring of clinical trials.

To gain buy-in from developing countries it has to be shown how they will benefit from the partnership and not be harmed for being seen as increasing regulation. This can be accomplished by discussions with developing countries that focus on the dual benefits of the partnership. As discussed, countries like India and China are quickly becoming large

¹⁵⁰ *International Programs*, FDA, <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/ucm291754.htm>. (last updated Apr. 22, 2014)

¹⁵¹ U.S. DEP'T OF HEALTH & HUMAN SERV., GUIDANCE FOR INDUSTRY AND FDA STAFF: GOOD CLINICAL PRACTICE: CONSOLIDATED GUIDELINE, May 9, 1997, <http://www.gpo.gov/fdsys/pkg/FR-1997-05-09/pdf/97-12138.pdf>, (The guideline is intended to define 'Good Clinical Practice' and to provide unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects).

¹⁵² *Supra* note 150.

pharmaceutical consumers as well. Showing how a partnership can protect individuals on both ends of the research spectrum, and how the risks that can occur when regulation breaks down far outweigh the risk of loss from increased regulation, will be difficult. This is true for two of the fastest growing pharmaceutical markets, India and China, are also two of the largest areas where clinical trials are conducted and fear that increased regulation will hurt their economy.¹⁵³ However, as discussed, the increase in harm to research subjects and questions on the validity of clinical data in India and China and their governments responses appear to open the opportunity for partnering. Further the tools developed in a good partnership can also be used to partner with new countries as the migration of clinical trials continues.

As discussed above in section A, the mechanisms for enforcement already exist.¹⁵⁴ Applying the regulations in the best, most efficient manner is what is needed.¹⁵⁵ Increased regulatory enforcement by the FDA, along with partnerships between domestic regulatory agencies will work together to put pressure on the industry to increase their level of self-regulation.

C. Peer to Peer Partnerships at Industry level

The biggest area for impact to prevent harm to research subjects and eliminate invalid clinical trials is at the industry level. Self-regulation at the industry level is also the area that is

¹⁵³ *India's Booming Drugs Industry*, THE ECONOMIST (Feb. 20, 2014 11:46AM), <http://www.economist.com/blogs/schumpeter/2014/02/indias-booming-drugs-industry> (“On February 10th Dr Hamburg signed a “statement of intent” with Keshav Desiraju, of India’s ministry of health and family welfare, to encourage collaboration between American and Indian regulators. But in a meeting with the FDA February 11th, India’s drug controller general cautioned against over regulation.”).

¹⁵⁴ *See supra* notes 140 and 141 and accompanying texts (discussing existing regulations for clinical trial data in foreign countries).

¹⁵⁵ *Id.*

most challenging. The industry is already highly regulated and places strict reporting requirements on sponsors of clinical trials.¹⁵⁶

Sponsors of clinical trials are required by statute following the determination that the investigational drug presents an unreasonable and significant risk to subjects to stop the trial and notify the FDA.¹⁵⁷ On paper this looks good, but in practice the results have been mixed.¹⁵⁸ Due to the high investment costs in R&D, the length of time associated with drug development and the financial impact at stake, responsible parties have shown that they are likely to look to the short term to recoup the R&D costs as soon as possible, at the risk of sacrificing the long-term health of a company, and it is easy to see why as sales of products have far exceeded fines for hiding clinical trial data and other regulatory violations.¹⁵⁹

What must be done is showing the industry why it is to their benefit to actively participate in preventing regulatory violations before they occur. The investment in compliance costs upfront is offset by reduction in compliance costs when the overall level of compliance is

¹⁵⁶ 21 C.F.R. § 312.56 (2013) (sponsor review of ongoing clinical trials includes taking corrective actions if it determines that the investigator is not conducting the trial according to the regulations and protocol); *see also* Mary Benadette Ott & Gary Yingling, SPONSORS' OBLIGATIONS, 2005 WL 4889080 (discussing the sponsor of a clinical trial responsibilities)

¹⁵⁷ 21 C.F.R. § 312.56 (d)(2013) (“notify the FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued.”).

¹⁵⁸ *See supra* notes 8, discussing CRO breakdowns and merck in china and vanity fair.

¹⁵⁹ Alexandra Sifferlin, *Breaking Down GlaxoSmithKline's Billion-Dollar Wrongdoing*, TIME (July 5, 2012), <http://healthland.time.com/2012/07/05/breaking-down-glaxosmithklines-billion-dollar-wrongdoing/>, (“Avandia...racked up \$10.4 billion in sales, Paxil brought in \$11.6 billion, and Wellbutrin sales were \$5.9 billion during the years covered by the settlement, according to IMS Health, “So a \$3 billion settlement for half a dozen drugs over 10 years can be rationalized as the cost of doing business,” [Patrick Burns, spokesman for the whistle-blower advocacy group Taxpayers Against Fraud].”).

raised.¹⁶⁰ The example discussed earlier of BMS self-reporting GCP violation during a trial of a blockbuster drug is a good example.¹⁶¹ An alternate scenario can be imagined where the violation was not reported, only for the violation to be discovered during the review process or after approval.¹⁶² The harm could have caused a longer delay in the approval time or caused the approved drug to be removed for the market. This would lead to a consumer loss in confidence in BMS, and cast further doubt on the industry practice of conducting clinical trials in developing countries. Instead, by reporting the violation, the approval time was only delayed nine months and investor confidence in BMS was not substantially harmed.¹⁶³

While the approach of not reporting has not been financially fatal, continued non-compliance will only raise the risk of permanent damage in developed and developing countries. Increasingly companies are becoming aware of this risk as evidenced by the industries exit from conducting clinical trials in India because of regulatory uncertainty.¹⁶⁴ This is evidence of the effort to lower R&D costs becoming potentially the culprit in alienating consumers from using their products in the emerging markets where the industry is increasingly reliant on selling its products.¹⁶⁵

Companies will be skeptical as they continue to compete over market share in developing countries. Further as new companies develop in these countries, they will not have the same self-monitoring expertise as established players and can create a problem that ends up giving the entire industry a black eye. The same goes for the large pharmaceutical companies who may be

¹⁶⁰ Frances Bruttin and Dr. Doug Dean, *Managing the Cost of Compliance in Pharmaceutical Operations*, (April 2004), p.8, file:///Users/mwjacobson/Downloads/managing-the-cost-of-compliance-in-pharmaceutical-operations%20(1).pdf

¹⁶¹ Armstrong *supra* note 109.

¹⁶² *Supra* notes 8, 159 and accompanying texts.

¹⁶³ Armstrong *supra* 109.

¹⁶⁴ *See supra* notes 109, 140 and accompanying texts.

¹⁶⁵ *See supra* note 8 and accompanying texts.

inclined to forego reporting a violation in the hopes of having potential revenues outweigh the regulatory violation costs.¹⁶⁶ What is needed is formalized approach that facilitates the understanding of the long-term benefits for industry stakeholders.

Organizations like the Association of Clinical Research Organizations (ACRO) and the Pharmaceutical Research and Manufacturers of America (PHRMA) can bring together industry participants to form agreements that work to increase compliance and self-report by sharing the costs of training and education in the area of clinical research. To increase compliance ACRO and PHRMA should explore membership agreements that place certain requirements on companies and include penalties for when violations occur.

The potential for this area is already displayed by instances of companies self reporting violations.¹⁶⁷ A more formal agreement would put the industry on firmer ground when it comes to the safety of clinical trial research and provide companies with incentive to cooperate.

Conclusion

The issue of protecting human research subjects and ensuring the validity of data from clinical trials continues to follow the pharmaceutical industry. It has followed the industry to each clinical trial location around the world. By looking at past mistakes the FDA, the pharmaceutical industry and international regulatory agencies can work together to protect human research subjects in clinical trials and ensure that the data outcomes are valid.

¹⁶⁶ *Supra* note 162 and accompanying text.

¹⁶⁷ *Supra* note 109 and accompanying text.