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INFORMED CONSENT: ENFORCING PHARMACEUTICAL COMPANIES' OBLIGATIONS ABROAD

Stacey B. Lee

ABSTRACT

The past several years have seen an evolution in the obligations of pharmaceutical companies conducting clinical trials abroad. Key players, such as international human rights organizations, multinational pharmaceutical companies, the United States government and courts, and the media, have played a significant role in defining these obligations. This article examines how such obligations have developed through the lens of past, present, and future recommendations for informed consent protections. In doing so, this article suggests that, no matter how robust obligations appear, they will continue to fall short of providing meaningful protection until they are accompanied by a substantive enforcement mechanism that holds multinational pharmaceutical companies accountable for their conduct. Issues of national sovereignty, particularly in the United States, will continue to prevent meaningful enforcement by an international tribunal or through one universally adopted code of ethics. This article argues that, rather than continuing to pursue an untenable international approach, the Alien Torts Statute (ATS) offers a viable enforcement mechanism, at least for US-based pharmaceutical companies. Recent federal appellate court precedent interpreting the ATS provides the mechanism for granting victims redress and enforcing accountability of sponsors (usually pharmaceutical companies and research and academic institutions) for informed consent misconduct. Substantive human rights protections are vital in order to ensure that every person can realize the "right to health." This article concludes that by building on the federal appellate court's ATS analysis, which grants foreign trial participants the right to pursue claims of human rights violations in US courts, a mechanism can be created for enforcing not only substantive informed consent, but also human rights protections.

INTRODUCTION

Over the last several years, the conduct of pharmaceutical companies sponsoring clinical trials abroad has come under increased scrutiny. This examination is due in part to concerns that companies are conducting clinical research overseas to avoid regulations and human rights protections that control domestic (US) research. Fuelling these concerns are civil lawsuits, criminal indictments, international investigations, and news exposés that have brought attention to human rights abuses that result from multinational pharmaceutical companies' ability to capitalize on the less stringent regulatory requirements in several developing countries.¹ The World Health Organization (WHO), United Nations (UN), and several higher-income countries are focusing on these regulatory disparities with the goal of better protecting the health and human rights of trial participants. While such efforts address several aspects of global clinical trials, informed consent is one of the most fundamental concerns in any discussion on human rights protections owed to individuals in medical experiments. In general terms, obtaining informed consent is a process that requires effective collaboration with researchers (those who generally conduct the trials), institutional review boards ("IRBs," which review

and approve clinical protocols before the trial begins) and sponsors (pharmaceutical companies as well as research and academic institutions). Informed consent requires researchers to convey to the subjects, in an adequate manner, the risks and potential benefits of the trial, their rights as participants, and their free choice whether or not to participate in a trial. Informed consent ensures protection of the human subject's "right to bodily integrity," that is, to "exercise sovereignty over her body."² When discussing human rights protections, the international framework — codes, declarations, covenants, guidelines, and laws — that articulates the informed consent obligations of nation-states and researchers in clinical trials is well defined. In contrast, the structures that articulate the obligations of sponsors are still developing.³

The first part of this article explores pharmaceutical companies' evolving informed consent obligations.⁴ In this section we first examine an event that brought into the public eye the globalization of clinical trials and the issue of informed consent — the case of Pfizer's controversial Trovan drug trial in Nigeria. We next summarize the legal and ethical background behind international and US approaches to pharmaceutical companies' informed consent obligations. The second part of the paper identifies methods through which current pharmaceutical company obligations can evolve to promote the "full realization of the right to health" as articulated in Article 2 about the International Covenant on Economic, Social and Cultural Rights.⁵ The paper concludes with a three-part discussion of how to enforce these obligations. It first challenges the suggestion that effective enforcement could come from an international tribunal or universal acceptance of one international code. It then provides an analysis of the Second Circuit's disposition of the case brought by the families and victims injured because of Pfizer's conduct in Nigeria.⁶ Finally, it concludes that the Second Circuit's analysis in the case, along with other precedent, can be expanded to provide a solution to the vexing problem of enforcement of human rights protections against US-based multinational corporations.⁷

PFIZER'S TROVAN CLINICAL TRIAL

In early 1996, an epidemic of bacterial meningitis broke out in the state of Kano, Nigeria. Bacterial meningitis is an infection of the meninges (the membranes around the central nervous system) that is diagnosed by the presence of infectious material and

other changes within the cerebrospinal fluid, and if not properly treated, can result in hearing loss, brain damage, or death. However, with early diagnosis and treatment, the risk of death is less than 15%.⁸ Doctors Without Borders/Médecins Sans Frontières (MSF), a nonprofit humanitarian organization, arrived in Kano shortly after the initial outbreak to provide humanitarian and medical aid. The organization began to treat the victims of the outbreak with the intravenous form of chloramphenicol, a WHO-endorsed generic antibiotic for bacterial meningitis in low-income countries.⁹

Within six weeks of hearing about the epidemic, Pfizer drew up a plan to test an oral form of the antibiotic trovafloxacin, trade-named Trovan, on the children in the Kano clinic.¹⁰ If the oral form of Trovan could be shown to be as effective as the intravenous antibiotics were for children, it would be a tremendous "breakthrough in battling epidemics" worldwide.¹¹ Children could simply swallow a pill rather than receive injections that increase the risk of blood-borne diseases, such as HIV and hepatitis.¹² Further, a pill would remove the need for skilled healthcare workers to administer the treatment. Wall Street analysts predicted that, if the Food and Drug Administration (FDA) approved the oral form, it would be a US\$1 billion blockbuster drug.¹³

On April 3, 1996, Pfizer's team of physicians arrived in Nigeria to conduct clinical trials on children infected with bacterial meningitis. Nigerian officials authorized Pfizer to conduct the testing in two wards of the Infectious Disease Hospital. Pfizer selected two hundred sick children from the many children who were awaiting treatment, divided the children into two groups, and treated one group with Trovan. The other group of children was "purposefully 'low-dosed'" with ceftriaxone, an FDA-approved drug.¹⁴ According to Pfizer protocol, the children were supposed to have their blood tested at the point when they were diagnosed and entered into the trial and again after five days of treatment. If a child was not responding well to Trovan, protocol required switching the child's medication to ceftriaxone. According to an internal Pfizer document, however, this plan for follow-up blood testing was generally abandoned "due to the shortage of medical staff."¹⁵ As a result, Pfizer did not analyze the children's blood samples and therefore could not determine those cases in which the medication was not an effective treatment until the child manifested visible and often permanent impairment.¹⁶

Pfizer protocol required injecting ceftriaxone into the subject's vein or muscle. Again, due to the shortage of skilled workers, the drug was usually injected into the child's buttocks or thighs (i.e., muscle injections) to save staff time and trouble. The shots were severely painful, leading to reports of "great fear and sometimes dangerous struggles with children."¹⁷ To lessen the pain after initial injections, the report indicated, researchers reduced the amount of antibiotic given to children who were improving to one-third of the recommended amount.¹⁸ Pfizer maintained that the reduced dose was more than sufficient. The drug's manufacturer, Hoffmann-La Roche, however, reported that the reductions could have lowered the drug's efficacy and skewed any comparison to Trovan.¹⁹ There is also evidence that Pfizer failed to switch to standard therapy the children who were receiving Trovan but not showing any signs of improvement. This breach in standard protocol allegedly led to severe brain damage or death for several children.²⁰

The requirement of informed consent from either children or their guardians is part of Pfizer's protocol and is also found clearly stated in a number of related international documents; these include the international human subject protections contained in the Nuremberg Code, the Helsinki Declaration, Article 7 of the International Convention on Civil and Political Rights (ICCPR), guidelines by the Council for International Organization of Medical Services (CIOMS), and certain WHO guidelines.²¹ However, Pfizer could not produce any evidence that its staff had informed the children's parents that the proposed treatment was experimental, that they could refuse it, that serious risks were involved, or that other organizations at the same site offered more conventional treatments for free.²² In addition, Pfizer failed to follow its own protocol that required staff to offer or read documents to participants in either English or Hausa to facilitate their informed consent. When interviewed later, many of the patients and their parents claimed that they did not know they were participating in an experimental drug trial. Pfizer described the lapse as a procedural error, but stressed in a written statement that "verbal consent was obtained."²³

After spending two weeks in the Kano camp conducting tests, Pfizer withdrew its personnel without administering any post-trial care. Five children who received Trovan and six children to whom Pfizer had administered a low dose of Ceftriaxone died. Others

suffered blindness, deafness, and paralysis.²⁴ While US medical guidelines recommend that meningitis experiments include long-term follow-up, Pfizer's clinical trial protocol made no mention of the need for long-term monitoring.²⁵

In 2001, the families of the dead and injured children filed suit against Pfizer under the Alien Tort Statute (ATS) for violating a norm of "customary international law prohibiting medical experimentation on non-consenting human subjects."²⁶ Specifically, Pfizer was sued for violating the principle of informed consent, refusing to provide the best treatment available when it supplied low doses of the drug approved by the FDA and when it failed to monitor the progress of the children in the study, and for its decision to conduct a trial using a medication that is known to cause liver damage in children.²⁷ What the families soon learned however — and arguably what Pfizer had known all along — is that neither international nor US law provided redress against American companies for human rights violations committed abroad. What follows is a discussion of how this fact is changing.

THE ORIGINS OF INFORMED CONSENT: A LEGAL OVERVIEW

Medical professionals have for centuries discussed concerns about the treatment of human subjects. Only recently, however, have these rigorously debated ethical notions and legal protections for human subjects been codified. The six guidelines currently regarded as most influential, internationally, include the Nuremberg Code, the Helsinki Declaration, the Council for International Organizations of Medical Sciences (CIOMS) Guidelines, Article 7 of the International Covenant on Civil and Political Rights (ICCPR), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practices (ICH/GCP), and the recently revised FDA's "Good Clinical Practices" (GCP) guidelines for foreign clinical trials.²⁸ While the contours of these guidelines vary somewhat, the primacy of informed consent is a constant in every scheme. Furthermore, these documents reveal several universally accepted components of informed consent — including an explanation of the nature and procedure of the trial in a language that participants can understand and a requirement that the researchers obtain informed consent without pressuring sub-

jects, i.e., ensuring that they understand that they are free to choose whether or not to participate.²⁹ Notwithstanding the clarity and general acceptance of requirements, a gap persists between the theoretical ideal of informed consent and the reality of its application in international clinical trials.

Nuremberg Code

The Nuremberg Code (hereafter the Code) was the first modern effort by the international community to create guidelines governing research on humans. The goal of the Code is to protect the rights of subjects and to prevent the “horrendous non-therapeutic, non-consensual” medical experiments conducted by Nazi researchers during World War II from recurring.³⁰ The Code states that in medical experiments involving human subjects, “voluntary consent of the human subject is essential.” The individual must be able to “exercise the free power of choice” and must have sufficient knowledge of the nature of the experiment to make an “enlightened decision.”³¹ The subject should be informed of the “nature, duration, and purpose... the methods and means, all inconveniences and hazards reasonably to be expected...and the effects upon his health or person which may possibly come from this participation in the experiment.”³²

The Code’s significance as the document that symbolizes the beginning of the systematic ethical treatment of human subjects in clinical trials is without question. Taken as a whole, however, the Code is a simple document that is ill-equipped to regulate the changing landscape of clinical trials. Chief among the Code’s limitations is that the obligation to follow its precepts falls only on the researcher. The Code does not address the conduct of organizations that sponsor clinical trials. Further, it does not contain criteria to evaluate the quality of consent, nor does it provide specific measures of enforcement to assure adherence to its requirements.³³ In addition, neither the United Nations nor the United States recognizes the Code as a binding legal document. In fact, in the United States, no court has ever awarded an injured individual damages solely for violation of the Nuremberg Code.³⁴

In the context of the Trovan clinical trial, an argument could be made, as the plaintiffs’ did, that Pfizer’s conduct violated the Nuremberg Code to the extent that its doctors did not obtain informed consent from the participants. Would the United States legal system

recognize, however, violations on international law that are contained in a document it never adopted?

Helsinki Declaration

In 1964, the World Medical Association established the medical community’s version of informed consent standards with the Helsinki Declaration (Declaration). Most recently revised in 2008, the Declaration strengthened the foundation of the Nuremberg Code by requiring that consent should “preferably” be in writing.³⁵ The Declaration also states that every patient — including those in the control group, if any — should be assured of the best proven diagnostic and therapeutic method.³⁶ Critics have argued, however, that drafters of the Declaration weakened the informed consent obligations by making them secondary to other concerns, such as the principle “that the individual human subject’s health is valued over competing gains to others, and . . . that the best treatment available is used.”³⁷ In addition, the Declaration weakened the Code’s universal free and fully informed consent requirements. According to the Declaration, these requirements are not needed in therapeutic research if the researcher believes that they are unnecessary or difficult to obtain. Moreover, physicians and researchers wrote this document primarily for themselves. As such, it places no requirements nor offers any guidance on the role of sponsors in clinical trials, much less their corresponding obligations to ensure informed consent protections. Yet, until 2008, the standard outlined in this Declaration governed all clinical trials sponsored by US-based pharmaceutical companies outside of the United States.³⁸

ICCPR

In 1966, the concept of informed consent gained international acceptance when the UN incorporated it into the ICCPR as a human right. Article 7 of this Covenant states that “no one shall be subjected without his free consent to medical or scientific experimentation.”³⁹ This obligation is legally binding on the more than 160 state parties. By its terms, the prohibition is not limited to state actors; rather, it guarantees individuals the right to be free from non-consensual medical experimentation by any entity, whether they are state actors, private actors, or state and private actors working together.⁴⁰ Accordingly, under the ICCPR, sponsors are liable for failure to obtain informed consent. While the ICCPR confers

absolute rights, it is not self-enforcing and has yet to be applied in any human rights lawsuit against a non-state actor.⁴¹ Moreover, while the United States recognizes the ICCPR's status, the ICCPR is not self-executing and does not create a binding international legal obligation that is enforceable in federal court. Accordingly, Article 7 of the ICCPR, though applicable to sponsors, cannot be used as a legal document for action in the United States.⁴²

CIOMS Guidelines

In 1982, WHO and CIOMS created the International Ethical Guidelines for Research Involving Human Subjects (the Guidelines).⁴³ Most recently amended in 2002, the goal of the Guidelines is to support and help implement the ethical principles of the Helsinki Declaration, "particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements."⁴⁴ The Guidelines identify 26 separate items of information an investigator must provide to trial participants prior to obtaining their informed consent. For example, the Guidelines require that the investigator inform subjects of the risks, benefits, aims, methods, alternative procedures or treatments available, and of his or her right to withdraw from the trial without penalties.⁴⁵ The Guidelines also obligate investigators to inform participants of their right to free treatment for injuries related to research and the right to compensation for accidental injury resulting from the trial. Unlike the vague notion of informed consent articulated in the Declaration, the Guidelines recognize the challenges presented by conducting trials in developing countries and require that physicians make "every effort" to ensure that individual consent is informed.⁴⁶

The researcher obligations contained in the Guidelines regarding clinical trials in general and informed consent in particular are exacting. In sharp contrast, there are no sponsor-specific informed consent obligations. There are, however, five shared sponsor/investigator consent responsibilities, including obligations to ensure that intimidation is not used, that consent is renewed if there is a substantial change in trial conditions or procedures, and that, generally speaking, consent is in written form.⁴⁷ Unlike the detail provided in the investigator obligations, the Guidelines give neither party any guidance regarding the satisfaction of these joint obligations. Similar to the Code and Declaration, the Guidelines are not legally binding.

ICH Good Clinical Practice

In an effort to facilitate the international harmonization and "mutual acceptance of clinical data by regulatory authorities," the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was formed. In 1997, this organization (composed of governmental and private industry representatives), in conjunction with WHO, created the "Good Clinical Practice" (ICH/GCP) standards. While human rights protections were not the impetus for the creation of these standards, the ICH/GCP is widely accepted as industry guidance for clinical trials involving human subjects. Signatories to the document include representatives of governmental agencies from the European Union, the United States, Australia, Canada, and the Nordic countries.⁴⁸

The ICH/GCP contains thirteen principles intended to ensure the safety of participants and the accuracy of data in clinical trials. The first principle states that "clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the GCP and applicable regulatory requirements."⁴⁹ In subsequent principles, the ICH/GCP refines the informed consent requirements contained in the Declaration. Specifically, the guideline identifies protocols for obtaining consent and disclosing required information to prospective trial participants.⁵⁰

The resulting standards separate out the roles and responsibilities of researchers, institutional review boards, and sponsors.⁵¹ In doing so, the document is the first set of international guidelines that recognizes sponsors as having specific obligations in clinical trials. Similar to the CIOMS Guidelines, it is specific in establishing investigator responsibilities. For example, the standards identify what information the investigator must relay to the participant.⁵² In addition, the ICH/GCP describes prohibitions against coercing or unduly influencing the subjects, mandates that the subject is afforded "ample time and opportunity to inquire about the details of the trial and to decide whether or not to participate," and ensures that all the subjects' questions about the trial are answered.⁵³ The guidelines also require researchers to describe how and when informed consent was obtained and provide a sample informed consent form.⁵⁴

Unlike the level of detail provided in other parts of the ICH/GCP, the principle that addresses sponsor

obligations is cursory at best. The ICH/GCP limits a sponsor's obligation to "implementing and maintaining quality assurance," verifying that "subjects are protected" and ensuring that investigators comply with GCP and regulatory requirements.⁵⁵ The ICH/GCP allows the sponsor to transfer all trial-related duties to a contract research organization. Thus, sponsors are not required to have any direct involvement in ensuring quality or human rights protections. While the standards create stringent requirements for informed consent, the daily responsibility for ensuring compliance remains with the investigator.⁵⁶ Accordingly, the majority of sponsor obligations are merely supervisory in nature. In 1997, the FDA adopted these standards as guidance but declined to incorporate them into mandated FDA regulations.

FDA Good Clinical Practice: One step forward, two steps . . .

In April 2008, the FDA issued new regulations for data from clinical trials conducted outside the United States.⁵⁷ While consistent with the ICH/GCP, they are not identical. The FDA standards require that clinical trial procedures, including informed consent processes, must adhere to the FDA's version of good clinical practice. Prior to this, the FDA required foreign data submitted for approval to comply with ethical principles expressed in the Helsinki Declaration or the regulations of the country where the research was conducted — whichever afforded greater protection.⁵⁸ The FDA states that one of the reasons for revising the guidelines was due to an "evolution of the standards for protecting human subjects."⁵⁹ In the preamble, the FDA notes, "Although the Declaration states that it is unethical to enroll human subjects in poorly designed or conducted clinical trials, it does not provide guidance on how to ensure proper conduct of trials."⁶⁰ The FDA's regulations echo the ICH/GCP's goal of creating a "standard for conducting clinical trials in a way that . . . the rights, safety and well-being of trial subjects are protected."⁶¹ The new requirements were designed to remedy the disparities in regulatory safeguards for human research subjects in many of the countries where companies conduct premarketing clinical trials. The new regulations set standards for foreign clinical trials that are more consistent with the requirements of comparable trials conducted domestically. The most significant aspect of the GCP is that not only are sponsor obligations in clinical trials clearly defined, but they are also, for the first time, substantial.⁶²

For example, the regulations require sponsors to provide documents demonstrating their compliance with requirements of the GCP and Independent Ethics Committee (IEC), "a review panel that is responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation . . ." ⁶³ When submitting data from foreign clinical trials to the FDA, sponsors are obligated to describe the methods for obtaining informed consent. Other sponsor obligations include providing a description of any incentives given to the subjects, describing how the sponsor monitored the study to ensure that it is carried out in compliance with the study protocol, and identifying the IEC as well as providing documentation of the IEC's decision to approve or modify the study.⁶⁴ The revised regulations also identify the lone circumstance under which sponsors are not obligated to obtain informed consent: life-threatening situations when the IEC has conducted a review prior to the initiation of the study and concluded that obtaining informed consent is not feasible.⁶⁵

However, criticism of the FDA's GCP is its self-admitted "flexibility." In drafting the GCP, the FDA refused to incorporate the ICH/GCP's detailed approach with respect to identifying responsibilities of various parties. For instance, the ICH/GCP has specific protocols that must be carried out by particular parties for reporting adverse events and monitoring trials. Instead, the FDA adopted regulations that are sufficiently malleable to permit countries to take one of any number of different approaches to regulate clinical research and obtain informed consent.⁶⁶ The extent to which that "flexibility" leaves the door open for continued human rights abuses remains to be seen. These issues and concerns are a reminder that, while advances have been made in the area of informed consent, work is still needed to ensure that meaningful human rights protections exist for all subjects participating in clinical trials.

THE EVOLVING OBLIGATION — WHERE TO NEXT?

The scope of those responsible for ensuring informed consent protections has evolved since its international inception in 1946. It has been argued that human subject experimentation is one of the few areas of health where the language of "rights" has evolved enough to have practical consequences.⁶⁷

There is a certain amount of truth in this assertion. For the countries that have adopted them, the ICH/GCP and revised FDA regulations require more specificity and accountability in obtaining informed consent than previous guidelines. In particular, the revised FDA guidelines require sponsors, rather than just researchers, to take active responsibility for ensuring proper informed consent procedures. These developments suggest that the gap between the theoretical ideal and the practical reality of informed consent protections may be closing. Though not entirely found in one document, many of the components of the fully evolved set of obligations for pharmaceutical companies currently exist. Drawing from those sources, Table 1 outlines what that set of obligations

might look like.

These obligations would require tighter US regulations that ensure more specificity in what information is given to subjects. On an international level, the obligations call for WHO and UN to hold pharmaceutical companies to the same level of accountability as investigators in acquiring informed consent. Finally, on the industry level, they necessitate pharmaceutical companies' willingness to accept responsibility for adverse incidents and compensation of victims without resorting to protracted litigation. However, for any of these current or proposed measures to have a meaningful effect, adequate enforcement mechanisms are necessary.

<p>Table 1: Realizing the right to health: Proposed pharmaceutical companies' informed consent obligations in pharmaceutical companies' informed consent obligations in clinical trials</p>
<p>Elements in evolved pharmaceutical informed consent obligations</p>
<p>Required disclosures to FDA</p> <ul style="list-style-type: none"> • Disclosures consistent with ICH E3 section 5.3 <ul style="list-style-type: none"> • Description of when and how informed consent was obtained * The FDA requires sponsors to make this disclosure when submitting clinical trial data from outside the United States. • Sample of informed consent form • Disclosures consistent with ICH E6 section 4.8 <ul style="list-style-type: none"> • Identification of who obtained the informed consent • Description of how informed consent was obtained – requires sponsor documenting the subjects were given information consistent with CIOMS/WHO informed consent requirements (see below) • Description of actions taken to address cultural, social, religious, or literacy issues that may affect informed consent
<p>Required disclosures to participants currently required in 45 CFR part 46; the FDA does not require sponsors to make these following disclosures in clinical trials conducted outside of the United States</p>
<ul style="list-style-type: none"> • Statement that the study involves research • Explanation of purpose of the study • Explanation of procedures to be followed • Description of foreseeable risks or discomfort • Description of any benefits to subjects or others • Disclosure of alternative courses of treatment • Confidentiality of records • Compensation for medical treatments in the event of injury • Next of kin notification in event of injury • Risks of injury to embryo or fetus • Costs to the participant

THE QUESTION OF ENFORCEMENT

Postscript on Trovan

The literature on informed consent often includes discussion on how to enforce the human rights protections of trial participants, or in the alternative, how to enforce actions against non-state actors who violate these rights. Many proposals struggle to adequately address the challenges to informed consent requirements created by multinational pharmaceutical companies conducting trials in countries with limited regulatory frameworks and/or inadequate human rights protections. For example, a frequently discussed solution is the creation of an international UN or WHO type tribunal that would have the authority to police international trials.⁶⁸ Under the terms of this proposal, all countries would recognize this entity, and participation in resolving disputes would be mandatory. Another suggestion has been to use the Agreement on Trade-Related Aspects of International Property Rights

(TRIPS) to deny intellectual property protections to pharmaceutical companies that have developed drugs through sponsored trials that violated the rights of trial participants.⁶⁹ Still others have suggested enforcement of human rights protections for trial participants that requires the universal and mandatory adoption of an ethical guideline like the Nuremberg Code or Helsinki Declaration discussed in this article.⁷⁰ The flaw in these proposals is their reliance on the creation of an international agency or law that could challenge national sovereignty.

In many developing countries, this enforcement vacuum creates insurmountable challenges for injured trial participants who are forced to look outside of their own country’s judicial system for relief against US-based clinical sponsors. In these situations, participants quickly learn that there is no internationally binding law; no international forum to assess the

Table 1 continued: Realizing the right to health: Proposed pharmaceutical companies’ informed consent obligations in pharmaceutical companies’ informed consent obligations in clinical trials

Required disclosures to participants required in 21 CFR Part 50 and ICH/GCP
<ul style="list-style-type: none"> • Pertinent new information will be given • Approximate number of participants • Trial procedures • Trial treatments • Subject responsibilities • Payment for participation • Who will have access to the data • Person to contact for additional information or in the event of injury • Duration of participation • May refuse to continue participation without risk of loss of benefits
Required disclosures in CIOMS/WHO
<ul style="list-style-type: none"> • Right to access their data • Benefits of research to society or community • Consequences of breaches in confidentiality • Use of genetic information • Sponsor name, institutional affiliation, sources of funding • Commercial benefits of and monetary benefits for specimen use • Extent of investigation responsibilities to provide medical services • Approval of research by ethics committee • Free treatment for injury • Compensation to family and dependents for disability or death • Role of investigator as investigator and/or participant’s physician

validity of a human rights infringement by a non-state actor, much less sanction the violator or compensate the victim; and a multitude of jurisdictional obstacles that threaten their ability to sue in the sponsor's country.⁷¹ The FDA's revised clinical trial guidelines offer little in the way of penalties for noncompliance and even less in terms of participant redress. For example, according to the GCP, if a sponsor's conduct violates the informed consent regulations, the trial data is still reviewed; it just cannot be used to market or sell the drug in the United States. If the sponsor's conduct injured or caused the death of a participant, the regulations do not require the sponsor to administer post-trial care, compensate participants, or in the event of death, compensate the participant's family.

Even the robust set of obligations proposed in the previous section is, in isolation, inadequate to guarantee a pharmaceutical company's compliance with informed consent requirements throughout the developing world. However, as illustrated in the Second Circuit Court of Appeals' ruling in the Trovan case, perhaps the answer to enforcing sponsor obligations and ensuring human rights protections can be found, not through regulatory agencies, but rather through the courts.

In the aftermath of Pfizer's departure from Nigeria, the victims and family members of victims wanted to file suit against the company. Among their first challenges was to find an appropriate forum. Unlike Anglo-American corporate law, international law generally does not consider corporations as "legal persons."⁷² Rather, the focus of international law is on systematic abuses of human rights and state interests and duties. Accordingly, violations of international norms by a corporation are seldom enforceable in an international human rights forum. Given the lack of a viable international forum, the plaintiffs pled their case under the United States' Alien Tort Statute (ATS).

The ATS was passed in 1789 as part of the Judiciary Act and provides federal courts with jurisdiction over claims by foreigners for civil wrongs (torts) committed "in violation of the law of nations."⁷³ Until it fell into disuse, the statute was largely applied to protect victims of piracy on the high seas. More than two centuries later, advocates in the United States are testing the scope of the statute to protect victims of human rights abuses abroad. In 1980, relatives of a Paraguayan who was kidnapped and tortured to death by a Paraguayan police official used the ATS to bring

a claim in the United States against the officer after he moved to New York City.⁷⁴ The Second Circuit's adjudication of that case opened the door to more foreigners filing ATS suits in the United States. In 2004, the Supreme Court's ruling in *Sosa v. Alvarez-Machain* all but closed the door on the applicability of the ATS to international claims. In *Sosa v. Alvarez-Machain*, the Supreme Court held that the ATS "was intended only to prohibit conduct for a moderate number of new international law violations that were sufficiently 'specific, universal and obligatory.'"⁷⁵ The Court further narrowed the applicability of the ATS by noting that the violation must "rest on a norm of international character accepted by the civilized world and defined with specificity comparable to the features of the 18th century paradigms we have recognized."⁷⁶

In the wake of that decision, the district court evaluated the Trovan plaintiffs' claims. In their complaint, the families relied on four sources of international law that prohibited medical experimentation on people without their consent: the Nuremberg Code, the Declaration of Helsinki, the CIOMS Guidelines, and the ICCPR. While the district court recognized that non-consensual medical experimentation violates the laws of nations, it held that this judicial determination does not entitle the plaintiffs to relief. Relying on its interpretation of *Sosa v. Alvarez-Machain*, the court held that the "law of nations does not create private causes of action to remedy its violations, but leaves to each nation the task of defining the remedies that are available for international law violations."⁷⁷ In turning to the claims of violations of international law grounded in the Code and Declaration that supported jurisdiction under the ATS, the court held that the non-binding nature of these documents "does not create a private right of action in US federal courts" and is "unlikely to give rise to obligations in any strict sense."⁷⁸

The court concluded its reasoning by noting that

a court is not granted a roving commission to pick and choose among declarations of public and private international organizations that have articulated a view on the matter at hand. Such declarations are almost invariably political statements — expressing the sensibilities and the asserted aspirations and demands of some countries

or organizations — rather than statements of universally recognized legal obligations.⁷⁹

As a result, the court dismissed the plaintiffs' claims for failing to provide a predicate for ATS jurisdiction.

On appeal, the Second Circuit reversed the lower court's decision and remanded the case back to the district court. In its opinion, the appellate court explained, the trial court misinterpreted the nature of customary international law and the required inquiry by *Sosa v. Alvarez-Machain*.⁸⁰ According to the court, determining whether an international norm is sufficient to bring a cause of action under ATS requires an examination of how the norm compares with 18th century paradigms, whether the world community accepts the norm, and whether States universally abide by the norm out of a sense of mutual concern.⁸¹

In finding that the plaintiffs' claims met that standard, the court held that

[h]istory illustrates that from its origins with the trial of Nazi doctors through its evolution in international agreements, declarations and domestic laws, the norm prohibiting non-consensual medical experimentation on human subjects has become firmly embedded and has secured universal acceptance in the world community.⁸²

In correcting the trial court's misapplication of *Sosa v. Alvarez-Machain*, the appellate court clarified that nothing in that opinion suggests that the ATS inquiry be halted "if some of the sources of international law giving rise to the norm are found not to be binding or do not explicitly authorize the cause of action."⁸³ Thus, after eight years of litigating whether US courts have jurisdiction to hear the case, the US Court of Appeals for the Second Circuit affirmed the plaintiffs' right to sue Pfizer in the United States. On January 30, 2009, the appellate court remanded the case to the US district court for a trial on these merits. On August 10, 2009, Pfizer filed a *writ of certiorari* (an appeal) to the Supreme Court to hear its appeal.⁸⁴ To date, the Court has not ruled.

The Second Circuit's solution to the enforcement problem

The significance of the Second Circuit's decision is twofold. First, it identified "informed consent" as a

universally recognized legal norm. Second, it permitted a lawsuit against an American-based pharmaceutical company for human rights violations. In doing so, the court articulated a legally enforceable framework for a foreign country's nationals to pursue clinical trial violations. This case also builds on the Second Circuit's application of the ATS to other human rights-related claims. In *Khulumani v. Barclay National Bank Ltd.*, the plaintiffs alleged that the defendants — more than 50 multinational corporations including Bristol-Meyers Squibb and Coca-Cola — actively collaborated with the South African government to perpetuate the repressive system of apartheid.⁸⁵ In reversing the district court's dismissal of the plaintiffs' ATS claims, the court of appeals explicitly extended its jurisdictional reach over international human rights violations.⁸⁶ These cases signify an important step in the advancement of universal rules of law condemning human rights abuses. By repeatedly affirming foreign victims' right to proceed with actions to redress wrongs and to hold companies accountable for human rights violations, whether those rights are explicitly codified in US law or not, the Second Circuit has increased the ambit of actionable ATS conduct.⁸⁷ Together, these holdings serve as persuasive authority in American courts.

Within the context of informed consent, the Trovan decision is instructive in terms of the gap that still exists between domestic and foreign trial participant protections. The court's holding suggests that sponsor conduct that violates protections afforded to trial participants in the United States or countries governed by the ICH/GCP but not prohibited by the GCP could be actionable under the ATS.⁸⁸ It is this potential for US pharmaceutical companies to face liability for human rights violations committed abroad, more than the change in regulations or international standards, that may hasten informed consent measures that offer true protection to clinical trial participants regardless of nationality.

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REFERENCES

1. Throughout this article, the term "developing countries" refers to countries with relatively low

standards of living and underdeveloped infrastructures. US Department of State, "The language of trade: Glossary" (Washington, DC: US Department of State, n.d.). Available at <http://www.4uth.gov.ua/usa/english/trade/language/glossdi.htm#devgco>. Recent articles have highlighted the lure of locating clinical trials in developing countries. Because of their impoverished governments' inability to provide medical treatment to their citizens, host countries (in Africa in particular) have little to no legislative protections for human subjects. As a result, the value proposition of developing countries to pharmaceutical companies is the ability to conduct clinical trials with minimal interference from regulatory bodies. The tacit agreement is that if the host country enacts laws or enforces international protections the pharmaceutical company dislikes, the company could simply move its resources to a less burdensome host country. M. Flaherty, "Testing tidal wave hits overseas," *Washington Post* (December 18, 2000).

2. F. Kelleher, "The pharmaceutical industry's responsibility for protecting human subjects of clinical trials in developing nations," *Columbia Journal of Law and Social Problems* 38/67 (2004), pp. 67–106.
3. According to the CIOMS Guidelines, the sponsor is often a pharmaceutical company that initiates, funds, organizes, and oversees the conduct of the clinical trial. The need to address sponsor conduct is a relatively recent concern born out of the emergence of for-profit organizations conducting clinical research in developing countries. Relocating trials to developing countries began after the 1980 FDA ruling that allowed data from foreign trials to be used in support of new drug applications. Flaherty (see note 1). This global expansion has brought with it a set of new unknowns related to sponsor conduct and possible exploitation of foreign subjects.
4. This article examines one of the many issues surrounding global clinical trials. This single focus does not suggest that inadequate informed consent protections are the most pervasive or egregious threats facing research participants. However, beyond the scope of this article, inadequate placebo controls, denials of standards of care, and lack of compensation for direct injury pose serious harm to the lives and safety of trial participants.
5. International Covenant on Economic, Social and Cultural Rights (ICESCR), G.A. Res. 2200A (XXI) (1966). Available at <http://www2.ohchr.org/>

[english/law/cescr.htm](http://www2.ohchr.org/english/law/cescr.htm).

6. The United States Court of Appeals for the Second Circuit is one of the thirteen United States Courts of Appeals. Its territory comprises the states of Connecticut, New York, and Vermont. It has appellate jurisdiction over the district courts in those regions. Available at http://www.uscourts.gov/court_locator/CourtMapDetails.aspx?state=NY.
7. Multinational companies are difficult to regulate. By using multiple facilities around the globe, corporations can strategically avoid state power and certain national regulatory schemes. For example, many of the FDA requirements regarding clinical trials do not apply outside of the United States. Moreover, to the extent that foreign trials must adhere to some FDA requirements, the agency lacks the resources to ensure compliance. Kelleher (see note 2), p. 84.
8. National Center for Infectious Diseases, "Meningitis." Available at <http://www.cdc.gov/meningitis/index.html>.
9. J. Stephens, "Where profit and lives hang in balance," *Washington Post* (December 17, 2000). The intravenous form of chloramphenicol used by MSF was recommended by WHO as the first line treatment for bacterial meningitis in low-income countries. World Health Organization, *Meningococcal meningitis*, Fact sheet 141 (February 2010). Available at <http://www.who.int/mediacentre/factsheets/fs141/en/>. At the time, however, ceftriaxone, was regarded in the industry as standard of care for bacterial meningitis. Federal Ministry of Health of Nigeria, *Report of the investigation committee on the clinical trial of trovafloxacin (Trovan) by Pfizer, Kano, 1996* (Kano, Nigeria: Federal Ministry of Health, 2001). Available at http://www.circare.org/info/trovan_clinicaltrialreport.pdf. In the use of ceftriaxone in its trial, Pfizer wanted to show that Trovan outperformed the FDA-approved industry standard, but the choice of ceftriaxone also demonstrates Pfizer's compliance with the rules governing human subjects research to provide standard of care.
10. Stephens (see note 9).
11. Ibid.
12. Ibid.
13. Ibid.
14. *Abdullabi v. Pfizer, Inc.* (2009), 562 F. 3d 163 (2d.

Cir), pp. 3–7.

15. *Ibid.*

16. *Ibid.*

17. *Ibid.*

18. *Ibid.*

19. *Ibid.*

20. *Ibid.*

21. *Ibid.*, pp. 22–23.

22. *Ibid.*, pp. 5–6.

23. *Ibid.*

24. *Ibid.*

25. *Ibid.*

26. *Ibid.*, pp. 4–5. The ATS grants US courts jurisdiction over claims brought by foreigners that constitute a violation of international law, as defined by Statutes of the International Court of Justice, art. 38 (1), June 26, 1945, 59 Stat. 1055, 1060, T.S. No. 993.

27. *Ibid.*

28. These sources are located respectively at (1) *United States v. Brandt, Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10* (Washington, DC: US Government Printing Office, 1949), vol. 2, p. 181–182 [hereinafter Nuremberg Code]. Available at <http://www.hhs.gov/ohrp/references/nurcode.htm>; (2) World Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, art. 20, 22, G.A. Res. (adopted 1964, amended 1975, 1983, 1989, 1996, and 2000). Available at <http://www.wma.net/e/policy/pdf/17c.pdf> [hereinafter Declaration of Helsinki]; (3) Council for International Organizations of Medical Services [CIOMS], *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, guideline 4 (3rd ed. 2002), superseding the 1993 second edition at guideline 1; (4) International Covenant on Civil and Political Rights, art. 7, Dec. 19, 1966, 999 U.N.T.S. 171 [hereinafter ICCPR]; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline for Good Clinical Practice

(ICH-GCP) *Federal Register* 62/90 (May 9, 1997) pp. 25692–25702; and Department of Health and Human Services, Food and Drug Administration, “Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application 21 CFR 312 [hereinafter GCP], *Federal Register* 73/82 (April 28, 2008), pp. 22800–22816. Available at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480537f08>.

29. Kelleher (see note 2).

30. H. Freyhofer, *The Nuremberg medical trial: The Holocaust and the origin of the Nuremberg medical code* (New York: Peter Lang, 2004), pp. 103–104.

31. The Nuremberg Code (see ref. 28).

32. *Ibid.*

33. *Ibid.*

34. A. Laughton, “Somewhere to run, somewhere to hide? International regulation of human subject experimentation,” *Duke Journal of Comparative & International Law* 18/181 (2007), pp. 118–212.

35. World Medical Association, Declaration of Helsinki. Available at <http://www.wma.net/en/30publications/10policies/b3/index.html>. The other revisions occurred in 1975, 1983, 1989, 1996, and 2000, with notes of clarification added in 2002 and 2004.

36. For further discussion, see B. Meier, “International protection of persons undergoing medical experimentation: Protecting the right of informed consent,” *Berkeley Journal of International Law* 20/513 (2002), especially pp. 526–529.

37. *Ibid.*

38. 21 C.F.R. §312.120 (c) (1).

39. *Abdullabi v. Pfizer, Inc.* (see note 14), pp. 37–39.

40. *Ibid.*

41. *Ibid.*

42. *Ibid.*

43. Council of International Organization of Medical Societies, *International Ethical Guidelines for Research Involving Human Subjects at General Ethical Principles*. Available at <http://www.cioms.ch/?frameguidelinesnov202.htm>.

44. Ibid.
45. Ibid., Guideline 1.
46. Ibid.
47. Ibid., Guidelines 1, 4–6.
48. ICH-GCP (see note 28).
49. Ibid.
50. Ibid., p. 25698.
51. Kelleher (see note 2), p. 76.
52. ICH-GCP (see note 28), p. 25698.
53. Ibid., p. 25697.
54. Ibid., pp. 25692–25702.
55. Ibid., p. 25702.
56. Kelleher (see note 2), p. 77–78.
57. Food and Drug Administration, “Human subject protection: Foreign clinical studies not conducted under an investigational new drug application,” *Federal Register* 73/82 (April 28, 2008). Available at <http://edocket.access.gpo.gov/2008/pdf/E8-9200.pdf>.
58. Ibid., p. 22801.
59. Ibid.
60. Ibid.
61. Ibid.
62. Ibid., pp. 22801–22811.
63. 21 C.F.R. 312.120(b).
64. Ibid.
65. 21 C.F.R. 312.120(c).
66. Federal Register (see note 57), p. 22810.
67. D. Otto, “Linking health and human rights: A critical legal perspective” *Health and Human Rights: An International Journal* 1/3 (1995), pp. 272–281.
68. See, for example, R. Yearby, “Good enough to use for research, but not good enough to benefit from the results of that research: Are clinical HIV vaccine trials in Africa unjust?” *DePaul Law Review* 53 (2004), pp. 1127–1154.
69. F. Khan, “The human factor: Globalizing ethical standards in drug trials through market exclusion,” *DePaul Law Review* 57 (2008), pp. 877–915.
70. R. Drinan, “The Nuremberg principles in international law,” in G. Annas and M. Grodin (eds), *The Nazi doctors and the Nuremberg Code: Human rights in human experimentation* (NY: Oxford University Press, 1992), pp. 174–182.
71. J. Ford and G. Tomossy, “Clinical trials in developing countries: The plaintiff’s challenge,” *Law, Social Justice & Global Development* (2004/1), pp. 3–17. Available at http://www2.warwick.ac.uk/fac/soc/law/elj/lgd/2004_1/ford/.
72. Ibid., p. 10.
73. *Abdullahi v. Pfizer, Inc.* (see note 14), pp. 14–15.
74. *Filartiga v. Pena-Irala* (1980), 630 F.2d 876 (2d Cir.).
75. *Sosa v. Alvarez-Machain* (2004), 542 U.S. 692, 732.
76. Ibid., pp. 732–733.
77. *Abdullahi v. Pfizer, Inc.* 2005 U.S. Dist. LEXIS 16126 (S.D.N.Y. Aug. 9, 2005), p. 26.
78. Ibid., pp. 33–34.
79. Ibid., p. 34.
80. *Abdullahi v. Pfizer, Inc.* (see note 14), pp. 24–25.
81. Ibid., p. 25
82. Ibid., pp. 48–49.
83. Ibid., p. 61.
84. *Pfizer Inc., v. Abdullahi*, writ of certiorari file to the Supreme Court of the United States, Docket No. 09–301 filed August 10, 2009. In a related matter, in May 2007, the state of Kano filed civil and criminal charges against Pfizer for the deaths in the Trovan case. After two years of negotiations, in April 2009, Pfizer agreed to pay the US\$30 million to the state, US\$35 million to the families and US\$10 million in attorney fees. In a separate action, in June 2007, the Nigerian federal government filed suit against Pfizer, its CEO and several of its employees seeking nearly US\$7 billion in damages for the deaths of children involved in the Trovan drug trial. In January 2009, the Nigerian federal government and Pfizer agreed to settle out of court. J. Stephens, “Pfizer Reaches Settlement in Nigeria Drug-Trial Case,” *Washington Post* (April 4, 2009).

85. *Khulumani v. Barclay National Bank, Ltd.* (2007), 504 F.3d 254 (2d Cir).

86. *Ibid.*, p. 260.

87. The ATS only provides an avenue for foreign victim redress in circumstances involving conduct that violates universally accepted international norms. In the area of human subject experimentation by nonstate actors, the necessity of informed consent is the only norm held to meet that standard. To that end, informed consent protections take on a “gatekeeper” type function. Neither the proposed sponsor obligations set forth in this paper, nor much Pfizer’s conduct in the Trovan case, void of an informed consent violation, could serve as a basis for filing suit under the ATS. The trend of future law, however, is unclear. Currently, the Trovan case is on appeal before the Supreme Court. I am hopeful that the Court will further expand the Second Circuit’s interpretation of ATS applicability in human rights cases to include redress in situations where valid consent exists but other abuses occurred.

88. *Abdullahi v. Pfizer, Inc.* (see note 14).