Clinical Drug Trials in the Developing World: Economic Incentives Drive Poor Ethical Oversight

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The history of clinical trials covers a wide variety of scientific, ethical, and regulatory challenges. This paper delves into the present ethical complications of clinical research within developing countries. Here the definition of clinical research is broad, encompassing all trials aimed at evaluating a medical intervention. In principle, the paper focuses on the exploitative nature of clinical trials in developing countries.

I argue that there are two primary mechanisms of exploitation. The first is a lack of properly obtained informed consent and the second is an inequitable distribution of post-trial benefits. Next, I argue that the reason malpractice has ensued is due to economic incentives of governments involved, leading to weak ethical regulation, and as a consequence, ethical uncertainty among researchers. While there are other contributing factors, such as economic incentives of researchers and Contract Research Organizations (CROs), as well as racial discrimination that deserve attention, my paper does not discuss them.

Throughout the paper, I draw from research conducted and analyzed around the world. Case studies supporting my claims are drawn from India, the US, and China. Research regarding informed consent is drawn from all over Asia, Africa, and Latin America. The Asian countries include Thailand, India, the Philippines, and China, while the African countries include Kenya and Tanzania. Finally, the Latin American countries include Colombia, Brazil, and Mexico.

Introduction

When research is conducted within developed countries, such as the US and Canada, there are strict ethical regulations reviewing clinical drug trials. When drug trials are conducted in developing countries, however, regulation is comparatively limited. As the cost of clinical trials rapidly rises within many developed countries, such as the United States, there is an increasing incentive to conduct research out of the country, where weak ethical regulation makes research more efficient and consequently, less expensive. In fact, 90 percent of new drugs approved this year were tested at least in part outside the U.S. and Canada (Robbins, 2017). As more developed countries start conducting clinical trials abroad, people are beginning to wonder how relaxed regulation may impact those involved.

Key to approaching my project has been asking, what motivates exploitation? Weak ethical regulation is arguably one of the most significant motivating factors. Ethical regulation includes the present guidelines, standards, and oversight provided by the governments involved to monitor clinical trials. By "weak" ethical regulation, I refer to a lack of enforcement of current regulations and insufficient existing ethical regulation. My focus on what creates relaxed regulation and how it has led to exploitation has been essential to my argument.

Who is Involved?

There are four groups accountable for exploitative malpractice. These are the physicians, the pharmaceutical companies, the countries hosting the research, and countries sponsoring the research.

1) The pharmaceutical companies are in charge of sending contract research organizations (CROs) to the country hosting the research. CROs are the businesses in charge of conducting research abroad.
2) The researchers/physicians are the people most directly accountable for not properly obtaining informed consent from research subjects. These are people working on behalf of both the country sponsoring the research and the CRO for which they work.
3) The governments hosting the research tend to be part of developing countries that have very relaxed GCP. GCP is an ethical standard known as Good Clinical Practice, which provides oversight to the CROs.
4) The countries sponsoring the research tend to be developed countries that have poor oversight abroad, enabling thousands of experiments to progress every year without thorough ethical review.

The Problem

Informed Consent

There are two mechanisms of exploitation present. The first is properly obtaining informed consent. By definition, informed consent is "a permission granted in the knowledge of the possible consequences, typically that which is given by a patient to a doctor for treatment with full knowledge of the possible risks and benefits" (Oxford Dictionary, 2021). It has its most important role in bioethics because it preserves the human rights of the subject to protection, autonomy, trust, self-ownership, and integrity, while also preventing abusive conduct and domination (Eyal, 2019). Without informed consent, subjects are enrolled in trials unknowingly. As a consequence, they are not only denied the right to say yes to a trial, but also the right to say no to unethical trials. It is then those subjects are left vulnerable to abuse.

While there are many ways to obtain informed consent, documentation is key for clinical trials. Documentation is important because it offers proof that consent was obtained. Based on a survey conducted across Asia, Africa, and Latin America from John Hopkins University, written consent was not used in nearly 40% of recent studies (Hyder, 2006). In other words, there is no record of consent for 40% of subjects.

A. Exploitation

Across my research, exploitation is defined as "procedural and outcome unfairness" (Hawkins, 2008, p. 251). When informed consent is not obtained in trials, pharmaceuticals benefit at the cost of the subjects' ignorance and possible injury, which is unfair and thus, exploitative by this definition. The injustice arises due to the lack of communication between the researcher and the subject regarding the risks of the trial, which may pose significant harm. It is important to note that the harm itself is not the source of the exploitation. If the subject acknowledges the risks involved and gives consent, then any harm induced is fair given the prerequisite, consent.

B. Ignorance

I would like to note a journal published by The Centre of Bioethics in Eastern and Southern Africa outlining "the therapeutic misconception" as a source of ignorance, one perpetuated by a lack of properly obtained informed consent. The therapeutic misconception is a belief by participants in a clinical trial that they are being given clinical care. The misconception is common among illiterate populations in developing countries (Mfutso-Bengo, 2008). As of 1995, many subjects believed that "an intervention [Drug trial] would not

be offered if it did not carry some promise of benefit" (Lidz, 2002, p. 59). This is problematic because while clinical trials have the potential to benefit a population, they certainly cannot promise it. As of 1983, Appelbaum found that as high as "70% certainly assumed that the intervention would not be offered if it posed significant risks" (Mfutso-Bengo, 2008, p. 1). Therefore, not only do subjects tend to assume that drug trials promise benefit, but they also tend to assume that drug trials promise little to no serious harm, making it clear that subjects are not receiving sufficient information regarding the risks of the trial. As of 2005 and 2006, the therapeutic misconception has been particularly prevalent among research participants in African populations (Mfutso-Bengo, 2008). How prevalent the misconception is around the world, however, is uncertain because it varies greatly depending on the circumstance in each trial. Nonetheless, the therapeutic conception, while a result of a lack of properly obtained consent, is also an indicator of it.

C. Abuse

I want to point out that there are extreme cases where without informed consent, tragic abuses have occurred, resulting in physical or psychological harm to the subject(s). The prevalence of these abuses, such as the use of placebos when there are alternative methods of treatment, however, are much less common. Quantitative studies on the percentage has yet to be found, but it is low. Nonetheless, the fact that these trials are able to proceed abroad and not in the United States illustrates that there is a risk of terrible abuse and thus, an urgent problem to address.

After an interview with a professor at the Stanford Law School, I concluded that even those informed may not understand the exploitative threat. Over email, Dr. Hank Greely, who specializes in Bioethics, states, "Although there are, from time to time, problems and even abuses, I don't think American drug testing in developing countries is generally unethical." When I read this, I understood the origin of his perception. Dr. Greely seems to dismiss the unethical nature of clinical trials because instances of extreme abuse are less common. I would like to point out that not properly obtaining informed consent leaves subjects vulnerable to abuse, making it an extensive ethical issue. Given that data suggests informed consent may not be obtained properly in 40 percent of trials across Asia, Africa, and Latin America, up to 40 percent of subjects could be vulnerable to more serious physical and psychological abuse. Therefore, just because terrible abuse does not always happen as a result of not obtaining informed

consent, people should not dismiss clinical trials abroad as generally ethical.

D. Case Studies

A Common Problem

To exemplify the issue, I will outline a short case study about a woman who has been exploited at the expense of clinical research. In May of 2009, a woman took her mother to a hospital because she began experiencing chest pains. As women in the bottom of the Hindu caste system, they were very grateful when the doctor told them that their treatment would be paid for by the government. What the mother did not know was that she was being enrolled in a drug trial because the doctor never had her sign a consent form. Unfortunately, within a few weeks, the woman began to experience even worse health problems, yet the doctor only urged them, "don't stop the doses" (Lloyd-Roberts, 2012). The woman did as she was told but died a few weeks. While this story may seem shocking, some seventy drugs similar to the one tested on the woman have been tested on over three thousand patients at this specific hospital in Indore, consent being swept under the rug.

A Less Common Problem

To exemplify the relevant, but less common problem, I will outline a short story about a clinical trial conducted in India in 2012, resulting in abuse. Since 2013, the rotavirus infection has been one of the leading causes of gastroenteritis and death in children worldwide. Thus, there was a very ethical motive in conducting trials abroad. Despite the availability of two vaccines proven effective in preventing rotavirus infections, however, more than 2,000 children in the trial received placebo injections of salt-water rather than one of the available effective vaccines. In doing so, researchers exposed subjects to risk of preventable, potentially fatal rotavirus infections (Carome, 2014). Such a study should not have been permitted in India, but poor oversight in developing countries has enabled them to progress with little ethical review.

Inequitable Distribution of Benefits

While many assume that clinical trials eventually provide medical care to trial subjects in desperate need of it and boost the economies of developing countries, both assumptions are often false. Only 32 percent of researchers surveyed even planned to distribute beneficial interventions to the entire study population upon its conclusion (Berkley, 2001). While participating in a study does not automatically entitle participants to the novel medication, it is arguably morally shameful not to treat participants upon the

conclusion of successful trials, especially when it is necessary to have a life threatening or debilitating pre-existing condition. The moral obligation is arguable because it is not tied to a contract, meaning that CROs are not breaking any legal obligation in not treating participants. The cost to treat many subjects can also be exorbitant, limiting what CROs can do to help the communities. However, I would argue that no effort to treat sick participants reflects not only carelessness for the community, but also an inherent unfairness for participants, who are essential to the progress of clinical research, but get little acknowledgement or care.

Unfortunately, clinical research often does not build the economy of developing countries. Not only do CROs fail to distribute the new drugs among participants, but they also fail to make it readily availability for the rest of the community. A survey commissioned by the national Bioethics Advisory Commission revealed that 48 percent of researchers abroad believe that it is unlikely that any drug created will be available to a host country residents (Berkley, 2001). In the journal, The Ethics of Global Clinical Trials, author Katrin Weigmann explains the reasoning behind why distribution can be difficult, noting new medications are often far too costly for people in developing countries to afford (Weigmann, 2015). Of course, this problem can be solved with time in some situations. While there are economic reasons why CROs choose not to make their drugs available in developing countries, however, it should arguably be an ethical duty of CROs to support the community in which they worked, especially when these organizations are making such a large profit. Without making any effort to give back to the community, the outcome deems unfair for the developing nations and is, therefore, exploitative in nature.

Economic Incentives

Below I explain how the economic incentives of governments involved have driven them to implement relaxed ethical regulation. I will first analyze the decisions of the countries hosting the research and then the decisions of the government sponsoring it, providing examples from China, India, and the US to support my conclusions.

The Host Country: GCP Standards

According to numerous sources, countries hosting research purposefully implement a more relaxed GCP to court foreign business. In some cases, research ethics committees in developing nations do not promote high standards of protection for participants in clinical trials due to lack of financial and human

resources (Burgess, 2012). However, foreign businesses, such as CROS, benefit from conducting research in countries with relaxed GCP because research is efficient and cheaper. Many countries hosting the research know this and implement a relaxed version on purpose although they have the financial and human resources to do otherwise. According to the International Center for Ethics, these decisions are often made on behalf of authoritarian regimes, corrupt local government officials, and health authorities eager to be paid off by first-world organizations (Kamau, 2010).

A. China

China's current GCP standards are highly relaxed, leaving room for exploitative behavior. China does not always require subjects to sign a consent form, only the investigator, and ethics regulations are not enforceable by law (Jacobson, 2014). Furthermore, evidence supports the fact that China's standard of GCP is purposefully exploitative in nature; whether it stems from economic motivations is uncertain, but instances of bribery validate that clinical research in China does favor pharmaceutical business. There are numerous instances where the Chinese review board has taken bribes to not report ethical violations. A notorious example is when the pharmaceutical company, GlaxoSmithKline, headquartered in London, paid over 490 million dollars to the R&D in China (Jacobson, 2014). The bribe was given so that the R&D would dismiss their unethical misconduct, such as their failure to record consent forms, in order to increase sales.

B. India

In India, there is great pressure to implement relaxed GCP for economic benefits. With lower costs, availability of large patient populations, and access to highly educated researchers, India provides great opportunity for western pharmaceutical companies struggling to cope with the rising costs of new drug development at home. Unfortunately, industry representatives say India will not be able to take advantage of its position unless it relaxes its rules governing clinical trials (Sharma, 2004). In 2004, the Confederation of Indian Industry, frustrated by slow regulatory review, called for "automatic approvals of all phases of clinical trials," if applications are not cleared within a time frame. Automatic approvals are problematic because they suggest a willingness to neglect regulatory review in order to promote pharmaceutical business. According to the Ministry of Health and Family Welfare in 2019, the government of India has allowed for the automatic approval of clinical trials if the review board has not granted approval within 30 working days (Government of India, 2019).

> However, these approvals are only granted to CROs that propose to manufacture and market the new drug in India, proving that the government has economic motivations in decreasing regulation.

The Sponsoring Country: Ethical Oversight

Using the US as a case study, I claim that countries sponsoring research may also be neglecting ethical oversight in favor of corporate interests. In the US, the FDA is in charge of providing oversight for clinical trials abroad. However, the FDA inspected less than 1 percent of the projects abroad (Ayalew, 2013; Hearn, 2011). The complete lack of oversight by the FDA suggests the US has purposefully abandoned its duty to provide ethical review. Here I argue that while the difficulties in applying an ethical framework abroad is multifaceted, it is in part, economic.

On the one hand, the FDA has been struggling to provide oversight as the growth of the clinical trial market has expanded abroad (Fisher, 2012; Jacobson, 2014). Providing review to all trials is simply not feasible. However, the FDA has demonstrated its economic motivations in relaxing ethical regulation through a decision it made in 2008. This decision was to reject the Declaration of Helsinki (DoH) for research abroad. The DoH is considered the benchmark of ethical and medical standards in clinical trials worldwide, even though it is not legally binding (Burgess, 2012). The FDA abandoned the DoH code after the World Medical Association decided to amend the code in 2000. Specifically, the DoH added new guidelines such as deeming placebo experiments when there is an alternative cure unethical and the distribution of new drugs mandatory in the host country (Burgess, 2012). When the FDA decided to abandon the DoH, it also abandoned the new best standard of medical practice – but only for research abroad. Critics point out that through this decision, the FDA has allowed for relaxed ethical regulation that specifically makes research for pharmaceuticals more efficient. As a consequence, the FDA has been criticized for favoring business incentives of American CROs (Anderson, 2008).

Ethical Uncertainty

To summarize the previous section, economic incentives of the legal system have motivated government officials to implement weak regulation. Moving forward, I want to unpack the question, *how has a lack of regulation lead to ethical uncertainty among researchers?* The primary reason without thorough ethical guidelines outlined in the host country GCP, researchers are forced to define these guidelines themselves. This is problematic because the ethical framework that worked in the US is often no longer

applicable within the cultural context of the foreign nation. Secondly, poor ethical regulation abroad has, as the New England Journal of Medicine highlights, enabled investigators to conduct research even when they are untrained and inexperienced (Kamau, 2010). As a result, researchers may not understand how to conduct proper ethics and are left ignorant of its importance.

Ignorance

Without thorough ethical regulation, there are two types of ignorance present among researchers and CROs. The first form of ignorance centers around how to properly obtain informed consent. In a journal written by two bioethics professors from John Hopkins University, a survey conducted across Asia, Africa, and South America, highlights that while most researchers, 69 percent of which had projects funded by the US, believe in the principle of informed consent, they disagree on what is sufficient in obtaining it (Hyder, 2004). Part of the uncertainty in sufficiency lies in the fact that how to obtain informed consent changes depending on the community**.** The International Center for Ethics further highlights the dynamic nature of informed consent as a problem, one making it difficult to obtain informed consent properly. Author AL Caplan explains that the meaning of informed consent might not be clear in a different cultural context, "where decisions are ultimately made by local leaders, religious figures, or husbands on behalf of their wives," (Caplan, 2010, p. 584). I would like to point out, however, the root of the problem does not lie in the dynamism of informed consent, but in the weak ethical regulation, which leaves researchers ill-informed about how to conduct ethical trials.

The second form of ignorance is that the validity of voluntary consent changes. I acknowledge that voluntary consent should be considered invalid depending on the circumstance of the community. Extreme poverty, for instance, is an important factor to consider (Emanuel, 2004). Extremely poor patients are often pressured to consent to clinical trials when they are compensated. Thus, participation may be necessary in order to have the money to put food on the table. These situations are named "no choice" situations where "willingness to participate" does not reflect a desire to do so, but a need to do so out of lack of other alternatives. Yet it appears that pharmaceuticals do not consider such situational factors as clinical research expands into poor and developing nations (Caplan, 2010). Instead of being a deterring factor, it has become one on which pharmaceutical companies can capitalize.

I want to draw some boundaries to my conclusions by making it clear that the presence of extreme poverty does not definitively make research in such a region unethical. When trials are held in poor countries, the risks of the trials are low, and

provision of benefits at the end of the trial are sufficient, then research in such communities may be advantageous. Yet considering the inadequate distribution of benefits today, and the lack of clarity regarding the risks of trials, research in such areas has predominantly promoted exploitation.

Overall, failing to consider the validity of informed consent is particularly problematic because there is also a risk that pharmaceuticals confuse 'willingness to participate' with 'ethical approval,' dismissing their unethical practice and deeming it 'good enough." It is then that pharmaceuticals may carry on with their exploitative behaviors in part because voluntary consent dampened their judgment of their malpractice.

Discussion

Across my research, ignorance has been a common problem for both participants and researchers. By working to mitigate ignorance across clinical research, exploitative malpractice will be greatly reduced.

One solution involves creating an ethical framework to define and guide researchers abroad on how to properly obtain informed consent. Creating an applicable framework will not be easy. In an interview with Dr. Holly Kathryn Tabor, an associate professor of medicine and bioethics at the Stanford Medical Center, she explains, "The most difficult part of obtaining informed consent outside of the US and Canada is working with population leaders to most appropriately address cultural norms and practices to ensure understanding and a lack of coercion." Thus, an ethical framework would need to be dynamic, or as Dr. Tabor later states, "consistent, but appropriate to the population".

I want to emphasize that conducting clinical trials in low-and-middle income countries is not inherently immoral. There is potential for heroic work. In the 1990s, ninety percent of the world's preventable mortality was due to untreated disease (Chuan, 2019). In response, pharmaceuticals honorably moved their practice abroad to save millions of lives. Clinical trials are a necessary part of introducing viable and safe drugs into the market. These tests, therefore, should be carried out in areas where the host community is likely to benefit. Unfortunately, the goals of such an honorable practice have been obscured in recent years as the allure of profit has cast a shadow upon the significance of ethics in clinical research.

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