GLOBALIZATION OF CLINICAL DRUG TRIALS AND FAILURE TO REGULATE

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ABSTRACT: United States' pharmaceutical companies often test their drugs in developing nations through the use of contract research organizations. Despite established ethical guidelines, questions arise of whether research in developing nations can be considered ethical. These questions surround the practice of using placebos, acquiring informed consent, and ensuring voluntary participation. Ethical guidelines such as the Belmont Report, the International Conference on Harmonisation, and the Declaration of Helsinki, outline important measures to promote ethical research, but they are rarely enforceable. In order to ensure ethical practices are being followed among drug trials, The Declaration of Helsinki must become enforceable and be recognized as the standard for ethical research in developing nations by United States' agencies and research institutions.

According to the Department of Commerce, the United States is the world's largest market for pharmaceuticals and is the leader in biopharmaceutical research. United States' firms carry out the majority of the world's development and hold the majority of rights on new medicines (Select USA, 2016). Yet, drug research within the United States has shifted, through the use of contract research organizations, to developing nations (Thiers, 2008). In the United States, great effort is placed on assuring ethical treatment of research subjects, but standards of ethical research vary among developing nations. This has caused ethical concerns regarding the use of placebos, informed consent, and voluntary participation among globalized clinical trials. Regulatory documents including the Belmont Report, the International Conference on Harmonisation, and the Deceleration of Helsinki, outlining ethical guidelines for clinical trials, have been put in place, but are not universal and rarely enforceable. In an effort to create ethical guidelines for international research, the Declaration of Helsinki was put in place by the World Health Organization and is by far the most comprehensive of current regulatory documents. Despite efforts to promote ethical research, globalized clinical drug trials cannot overcome these ethical dilemmas until the Declaration of Helsinki becomes enforceable and is recognized by United States research institutions and agencies.

The Shift of Clinical Trials to Developing Nations

Testing drugs for safety requires an extensive research process. For instance, the Food and Drug Administration (FDA) requires four phases of testing on human subjects. In Phase I, the drug is tested on healthy individuals for safety. In Phase II, the drug is tested on mostly healthy and a few sufferers of the disease of interest. Phase III involves the recruitment of a large number of individuals. who have the disease of interest and tests the drug's efficacy. During Phase IV, the drug is licensed for use but is closely monitored (Okanta, 2014). As the number of drugs produced rises, the number of clinical research participants in the United States decreases. Since 2002, the number of active FDA-regulated researchers, based outside the United States, has grown by fifteen percent annually, whereas the number of U.S.-based researchers has declined by five percent (Glickman et al., 2009). One study conducted by Glickman et al. (2009) found one-third of phase three clinical trials were being conducted

outside the United States.

This decline is partly due to the number of drugs each American is exposed to. Drug companies cannot test their drug on an individual who has been regularly exposed to medications, such as the average American, because it will cast doubt on the drug's ability to perform its intended purpose (Glickman et al., 2009). Due to a lack of research participants in the United States, drug companies have expanded their research past the United States border. (Petryna, 2005).

Another causal factor for globalized American research is the increase in clinical regulations in the United States making research costly. The added costs to clinical research has depleted government funds and placed a burden on researchers in the United States. As a result, American pharmaceutical companies have moved their clinical trials outside of the United States where trials are less costly. For instance, research in India at a first rate academic medical center is one-tenth the cost of running a trial in the United States (Glickman et al., 2009). Due to the various regulations by the U.S., the international community, and developing nations on human research, drug companies turn to contract research organizations to carry out their trials abroad.

When a drug company is ready to test their drug in a developing nation, they seek out a contract research organization (CRO). These organizations specialize in international clinical drug trials. They are responsible for finding a location, a population, and the health care professionals who will carry out the study. They are also responsible for knowing the local regulations for human research, the international regulations, and those of the United States. CROs are able to fill clinical trials quickly in places where treatments are limited and disease is prevalent. (Petryna, 2005) Globalization of clinical drug research and the use of CROs have raised ethical questions regarding the use of placebos, informed consent, and voluntary participation.

Ethical Implications of Globalized Research

Placebos

When conducting randomized experimental trials, it is common practice to use a placebo for the control group, but this is only ethical if there is no existing treatment (Angell, 1997). It is also standard practice, and more ethical, to use an existing drug as the control, if one exists. This ensures the control group is still getting treatment while acting as a control for the experimental group, yet this method has repeatedly been ignored because results are not as credible as that of a control-placebo study (Glickman et al., 2009).

Particularly in the 1990s, the use of placebos was in question due to HIV research in Africa. In 1994, American drug companies were testing their HIV drug, AZT, on pregnant women and using placebos for the control group. These drugs were designed to prevent the transmission of HIV from the mother to the fetus. At that time, existing HIV drugs were being used in the United States, yet researchers chose to use placebos over these existing drugs (Petryna, 2005). Both FDA and National Institute of Health officials supported the use of placebos to create greater confidence in the research results (Glickman et al., 2009). This created concern over the ethicality of using placebos and created a need for regulations specifically addressing placebos.

Informed Consent

Another ethical concern regarding the globalization of clinical drug trials, is the reliability of informed consent when language and cultural barriers are in place. For consent to be informed, the participant must know all the risks associated with the clinical trial and must be informed of their right to end their participation in the study at any time. This is difficult in developing nations where there may be barriers such as literacy, education levels, and cultural differences. The researcher may explain details of the study, but this is not always a good indica-

tor the participant understands the information. Another difficulty with informed consent is the inferiority some research subjects may feel. Researchers are often seen as superior due to their educational background and their ability to offer lifesaving treatments. This may deter participants from asking questions or exercising their right to end their participation at any time during the study. In this case, consent is not truly informed (Angell,1998).

Voluntary Participation

The expansion of research to the developing world has raised questions of whether participation is truly voluntary. Cases of individuals' involvement in research studies without their knowledge have led to strict guidelines in the United States over voluntary participation in research. These include caps on how much participants can be compensated for their participation (Belmont Report, 1979). If compensation is too high, it becomes impossible to decline participation in clinical trials. Institutional review boards in the United States screen studies for high compensation, but many globalized clinical trials are not screened at all or in this way. In some studies, participants are given incentives greater than their annual income and the study is their only opportunity to get medical treatment (Glickman et al., 2009). This creates a situation where participation in the study is not actually considered voluntary.

In some cases, participants are not even aware they are a part of a study. In 2008, the Center for Research on Multinational Corporations released a document of the detrimental results from globalized clinical trials in the 1990s and 2000s. Studies included participants from Uganda, India, and others who experienced adverse effects, and even death, who were not aware they were given experimental drugs. Even after these adverse effects were noted, most trials were allowed to continue (Kelly, 2013). The ethical implications of cases like these are staggering and clearly represent a need for ethical regulatory guidelines.

Current Regulatory Guidelines

The Belmont Report

The Belmont report outlines three basic principles for ethical research including respect for persons, beneficence, and justice. These principles represent informed consent, assessing risks and benefits, and the protection of vulnerable populations when selecting research subjects. While this document is the standard for scientific research using human subjects in the United States, it is not always enforceable.

According to the Department of Health and Human Services, the Belmont Report does not make recommendations for how it should be enforced, but is meant to be the standard adopted by institutional review boards and government agencies (Belmont Report, 1979). This becomes increasingly difficult in developing nations where research is not subjected to review boards. In a study by Glickman et al. (2009), only 56% of the 670 researchers surveyed in developing nations reported their research had been reviewed by an institutional review board. Another strategy for enforcing these regulations involves strict publishing guidelines. Medical journals make application of these guidelines a requirement for publishing, but many researchers employed by CROs from developing nations, are not aware of these guidelines and do not wish to publish (Glickman et al., 2009). For these reasons, the Belmont Report is not always applicable to globalized clinical trials.

The International Conference of Harmonisation

The International Conference of Harmonisation (ICH), which included representatives from Europe, the U.S., and Japan, put a set of guidelines for international research in place in 1990. The guidelines focus on the safety of the drug itself, the manufacturing process, and streamlining drug approval among nations. Although necessary, the ICH does not address ethical concerns regarding the selection of participants or the protection of the vulnerable (Singh, 2015).

The Declaration of Helsinki

The Declaration of Helsinki, developed by the World Medical Association, is the most comprehensive and detailed as it is aimed toward protecting research subjects in developing nations. It includes ethical principles outlined in the Belmont Report, but also adds a specific provision that every drug trial participant is entitled to the best medical care and treatment available at the end of the study. It also requires all clinical trials be subjected to an ethics committee. Finally, the Declaration of Helsinki forbids the use of placebos if existing drugs are available, but just as the Belmont Report is not always enforceable, neither is Helsinki. (World Medical Association, 2013)

Conclusions and Call to Action

The Declaration of Helsinki is a starting point for turning the tide toward ethical international research. Globalized research has the potential to spread advanced medical treatments to those who need them all across the globe, but serious changes must occur for this potential to be realized, including clear expectations that researchers conform to these guidelines in order to market their drugs or publish their research. This would require a regulatory institution with the power to enforce regulations.

The tragic abuse of research subjects throughout history has created a strong case for regulations on research. In an effort to promote ethical research, various guidelines have been prepared including the Belmont Report, the International Conference of Harmonisation, and the Declaration of Helsinki. Despite these guidelines, ethical issues surrounding the use of placebos, informed consent, and voluntary participation have occurred because these documents are not always enforceable or recognized by all nations. In order for globalized clinical trials to meet these ethical standards, the Declaration of Helsinki must become universal and enforceable. This would require a regulatory institution with the specific intent of regulating international research and drug trials. In the meantime, there must be a push for U.S. agencies to accept the Declaration of Helsinki as the standard and required regulation for international drug trials. There must also be accountability through the publishing of clinical trials and their results conducted in all nations. This would not only provide the public access to how research participants are treated, but would also make medical research open for everyone, the developing world included, to benefit from.

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