The John M. Rezendes Ethics Essay Competition

THE ETHICS OF THE UNITED STATES' CLINICAL TRIALS IN INDIA

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(Molecular and Cellular Biology)
2013

Clinical trials are one form of clinical research in which a new medication or other intervention is tested on human participants in order to observe its effect on the patient's health ("Learn About Clinical Studies," 2012). These tests help determine the safety and efficacy of the treatment before it becomes available for public use ("About Clinical Trials," 2011). Federal government agencies or pharmaceutical companies sponsor clinical trials with a primary investigator -- who might be a medical professional -- at the head of the trial ("UMClinicalStudies," 2010). Clinical research itself raises ethical issues due to the possibility of unsafe trial medications, but there are additional questions of morality surrounding the process used by clinical researchers. Each year, the percentage of clinical trials performed in developing countries increases. India in particular has become a hot spot for clinical research, with an increase from 40-50 trials in 2005 to 1,852 trials in 2011 (Yee, 2012). This situation between the United States and India can be used as an example to determine the morality behind the current process of clinical research. After closely examining the unequal relationship between the two countries involved in the trials, I believe it is immoral for the United States to perform clinical research in India using the current typical protocol.

The number of clinical trials in India has significantly increased over the past decade or so for several reasons. First of all, there is a 40-60% reduction in cost per person per trial when the research is conducted in India as opposed to in a developed country such as the United States (Yee, 2012). Due to the economy in India, compensation for participation can be very low while still acting as a sufficient bribe to participate (Ezekiel, 2004). Often, clinical researchers are able to evade offering compensation entirely (Cressey, 2012). In addition, many Indians have never been

exposed to medications ensuring that no previous treatments could potentially interfere with the test ("The India Opportunity"). Performing clinical trials in India is also beneficial for clinical researchers because the Indian health care system is poorly constructed and therefore is of low quality (Ezekiel, 2004). This generates a desperate need for treatment among patients causing more to participate in trials. Also, researchers only need to provide health care to participants as good as this existing low quality care (Ezekiel, 2004). Furthermore, Indian officials only weakly enforce the laws regarding clinical trials (France-Presse, 2013). Clinical researchers are able to take advantage of this unorganized structure to increase the convenience and decrease the cost of clinical trials. However, there is very little benefit to the Indians themselves as this research nearly entirely benefits developed countries (Allesandro, 2001). Due to the unequal distribution of power in this situation, it is clear that there are questions of morality that must be closely examined.

Care ethics will be used to analyze the morality of the United States' clinical trials in India and to develop possible solutions to the immoral practices. In the context of this theory, "care" refers to assistance given to individuals in order to ensure they have everything needed to live and to alleviate undesirable pain (Sander-Staudt, 2011). Analyzing a situation from a care ethics perspective requires examining the relationships composing the situation of interest. These relationships are not equal and include a dependent and an independent side, with the dependent side at risk for being taken advantage of due to its vulnerability, weakness, and lack of power and resources. Care ethics emphasizes that one must refrain from causing harm to another human being while interfering when an abusive relationship is evident and not harming a third group

throughout this process (Pettersen, 2011). With respect to international relationships, care ethics emphasizes the fact that the relationships between countries are unequal. Care ethicists do not strive to create identical situations in all countries but rather believe it is important that people attempt to alleviate the inequalities between countries in unbalanced relationships. One particular feminist care ethicist, Fiona Robinson, does not believe it will ever be possible to completely eliminate all inequalities in the world, but rather stresses the fact that by looking through the lens of care ethics, alternative solutions to global inequalities may be found (Sander-Staudt, 2011). It is therefore through this lens that clinical trials in India will be examined to determine their morality.

Despite the recent increase in the number of clinical trials performed in India (Yee, 2012), 90% of all clinical research currently performed in India benefits only 10% of the world (Allesandro, 2001). This is an example of the unequal distribution of international power between the developing (ex. India) and developed (ex. United States) countries. Therefore, while some people argue that clinical research is ethical because guidelines require that the research directly benefit participants (Ezekiel, 2004), this is clearly not the case in reality. Also, while clinical researchers are supposed to follow a set of regulations when performing research, limited regulation in India allows the United States to easily coerce Indians to participate in their trials even without following all the proper guidelines (Cressey, 2012).

In India, there are only three branches of the Drug Controller General (similar to the FDA in the United States) (Vaidyanathan, 2012), there is a corrupted and weak health care system (Yee, 2012), there are unclear documents outlining research protocols (which are easily interpreted in the favor of the researchers (Allesandro, 2001)), and there is

limited review of clinical research by ethical review committees (Cressey, 2012). Therefore, the relationship between the United States and India is unbalanced, leading to an immoral situation. Examining this situation using care ethics principles allows us to find several potential solutions to equalize the existing inequalities.

With only three Drug Controller General (Kahn, 2006) and the Central Drugs Standard Control Organization (CDSCO) (Vaidyanathan, 2012) in India, there cannot be adequate regulation of the kinds or safety of drugs administered during clinical trials. In fact, it has been revealed that the Drug Controller General has administered drugs that have not been adequately tested and therefore have not been proven to be safe. For example, a parliamentary committee analyzed forty-two randomly selected drugs administered in India and found that three did not have valid documentation while eleven others never went under phase III clinical trials (the final round of clinical trials (Kahn, 2006)). In addition to this, thirteen of them are not allowed in developed countries as they contain more than one type of medicine, promoting bacterial resistance. This is only supposed to be allowed in emergency situations, but it has been found that the CDSCO permits this in a new medication about once every month (Vaidyanathan, 2012). In addition to this, the Drug Controller General is not composed of people with medical qualifications. Because of this, they are supposed to acquire information about the safety of drugs from medical professionals, but a report committee found that in May 2012, this was not done for 64% of cases in India (Sreelata, 2012). This is a significant problem because it jeopardizes the safety and health of the Indian citizens. Also it allows for clinical researchers to carry out trials with very few regulations. Sometimes even, the hospitals where the tests are performed are branches of the pharmaceutical companies

sponsoring the trials, providing an easy access for corruption and little regulation (Kahn, 2006). The health care system of India is corrupted as well, as doctors are easily persuaded to recruit clinical trial participants. Large pharmaceutical companies often use bribes such as money and/or vacations to gain this participation. For example, Kalantri, a doctor at a hospital in Sevagram, India says that pharmaceutical companies will often give money or vacations to Europe or Hawaii to a doctor if he/she acquires participants for the trials (Kahn, 2006). In addition to this, pharmaceutical companies will often pay such a large sum for participation that any fines the doctor may have to pay for not following regulations are negligible. For example, in Madhya Pradesh, India, doctors not following proper regulations were fined only $100, but others who recruited participants for seventy-three trials received $1.02 million from the pharmaceutical companies for the recruitment (Yee, 2012).

Furthermore, the health care system in India is not well developed. Therefore, Indians may participate in the trials simply because there is a possibility of acquiring treatment for currently untreatable diseases (Allesandro, 2001). In addition, it is commonly believed that health care provided by the researchers must only be of at least equal quality to the health care available in the country where the research is being performed (Ezekiel, 2004). Since the health care in India is of poor quality, clinical researchers do not need to spend additional money providing decent health care to participants, as they would be required to if the research were performed in a developed country. However, it is only ethical from a care ethics point of view for better health care to be made available to participants. In care ethics, "care" is defined as assistance offered to help a particular problem that the people receiving the care are not able to solve

themselves (Sander-Staudt, 2011). Since Indians do not have the technology or finances to obtain better medicine and because the researchers and pharmaceutical companies do have access to these, it is only ethical for them to provide this care to the participants.

The poor health care system allows the researchers to use placebos in clinical trials. Placebos are extremely beneficial to a study because they enhance its scientific merit (Wang, 2003). Based on the newly revised Declaration of Helsinki (the document outlining ethical regulations of clinical trials) the researchers must test the new treatment against the best current available treatment. However, when no treatment is available in the country, placebos can be used instead ("WMA Declaration of Helsinki," 2013). Since this is the case in India, placebos can be used while still adhering to the Declaration of Helsinki (Allesandro, 2001). This contributes to the alluring aspects of India as a location for clinical trials, but this is unethical because the location of clinical trials should be chosen in a caring way to result in assistance to the participants, not simply based on ease. Even just the use of placebos itself (while still technically allowed by the Declaration of Helsinki in situations such as this) has negative effects on the participants, contributing to the uncaring practices of the trials. Participants may not realize that they might not receive the medication when participating in the trial. This is often either not explained to the volunteers or they may not understand it due to language or cultural barriers (Kahn, 2006). Therefore, one reason for participating in the trial -- to have the possibility of being cured of the disease -- is no longer relevant if that participant happens to be the person administered a placebo. In addition, even if the trial medication is successful and other participants are cured, those that are given the placebo often do not receive compensation (Cressey, 2012).

The Declaration of Helsinki includes several other clauses that are not clearly defined. Because of the lack of clarity, the pharmaceutical companies and clinical researchers are able to interpret these clauses in ways that make the trials easier, cheaper, and faster but that are uncaring for the participants.

Section 33 of the Declaration of Helsinki states that after the trial the best treatment as proven by the study must be made available to all participants ("WMA Declaration of Helsinki," 2013). Some people argue this falls under the responsibility of clinical caretakers, not the researchers (Ezekiel, 2004). However, as discussed previously, it is only moral from a care ethics point of view for the United States to provide this care to the Indians as the United States has access to the essential technology and finances for medical improvements and the Indians do not. To adhere to Section 33, the pharmaceutical companies and researchers do technically make the medication available to participants, but only for a much higher price than what the majority of them can pay (Allesandro, 2001). In a trial of a cardiac drug, for example, about 8,000 patients at the hospital in Sevagram, India participated. However, the final drug cost 800 rupees a day, more than any of the participants could afford (Kahn, 2006). Also, Section 33 does not state for how long the treatment must be provided (Allesandro, 2001) and pharmaceutical companies and researchers can use this lack of clarity to only provide the treatment for a short amount of time. Sections 22-26 of the Declaration of Helsinki describe the necessity of acquiring informed consent from every participant in a clinical trial. This is a very important aspect of the trial because only with the participant's full consent can tests performed on them not be considered harmful and unfair. In developing countries, the desperate need to be treated with no current available medication may drive a person to

participate in a clinical trial even if he/she otherwise would not. Because this consent is heavily influenced by the dire need to be treated, this cannot truly be considered voluntary. Furthermore, certain elements of the trial, such as placebos, may be challenging to describe to participants (Allesandro, 2001) and therefore a person may participate while unknowingly not understanding all aspects of the trial. In addition, it is difficult to determine from which level the informed consent should come (Allesandro, 2001). One doctor in India who works at a hospital in Sevagram said that nine out of ten times, his patients ask him to decide about their participation (Kahn, 2006). Therefore, this consent does not come from the participant him/herself and it is questionable about whether or not that can be considered voluntary. Due to these various interpretations of the Declaration of Helsinki in combination with a lack of regulation, many trials are performed without acquiring true informed and voluntary consent from individuals. A report was recently released giving proof of over 200 incidents where a participant had not given consent to participate in the clinical trial (France-Presse, 2013).

Section 25 of the Declaration of Helsinki states that informed consent does not need to be obtained when it is not possible or practical or when it would disrupt the results of the study. While research ethics committees must specially approve these situations, India is not under tight regulation and this approval could easily be bypassed. In addition, this clause does not clearly define “impossible” or “impractical” ("WMA Declaration of Helsinki,” 2013). Making the decision about whether or not a study qualifies for this therefore becomes a very subjective decision. Furthermore, the Declaration of Helsinki itself is not very forceful about researchers following these principles -- Clause 2 states that the document is addressed to physicians, but the World

Medical Association (WMA) “encourages” anyone carrying out medical research to follow these guidelines as well ("WMA Declaration of Helsinki,” 2013). The lack of force in this statement could cause a researcher who is not directly a physician to disregard the Declaration entirely. This would result in an uncaring trial in which the participant’s rights were not respected.

The Belmont Report is another document outlining ethical practices for clinical researchers. However, this report states that while it can be used to help solve ethical problems in clinical research, every situation is different and will require some subjective decisions. This can create more ethical problems because, as with several unclear clauses in the Declaration of Helsinki, it leaves room for multiple interpretations. The first ethical principle discussed in the Belmont Report is the principle of respect. Under this principle, there is a distinction between people who can make their own independent, informed decision about participation in a study and those who are unable to make this decision independently and should therefore be protected. While Indians are independent, as discussed previously their decision to participate in the trial is heavily influenced, making this a tricky situation to define based on the principle of respect. The Belmont Report also discusses the fact that harming another individual, as can be the result of an unsuccessful trial, is never ethical except for when this harm will be beneficial to many others. However, based on care ethics, under no circumstance is harming another human being ethical. Because of the current ethical issues in the way clinical research is performed in India, future benefit from the trial is acquired only through immoral and uncaring practices that can never be outweighed by a successful treatment found in the study. Furthermore, the Belmont Report specifically states that because of the principle of

justice, the successful treatments from the research must be made available to the participants and must not be too expensive for the participants ("The Belmont Report"). However, as discussed previously, this is not always the case. Similarly, the Belmont Report emphasizes the fact that researchers must be particularly careful when testing members of vulnerable populations and that the reasons for selecting a certain population must be justified, meaning this population enhances the research in a unique way ("The Belmont Report"). However, India is chosen as a location for research because of the ease and inexpensiveness of the clinical trials, not because Indians themselves as subjects enrich the research. These situations are proof that although there are some aspects of documents such as the Belmont Report encouraging for ethical, caring practices in clinical trials, poor regulation in clinical trials often causes their guidelines to be ignored.

Ethical review committees have the purpose of ensuring that all aspects of clinical research uphold outlined ethical guidelines and standards (Chin, 2011). However, there is very little oversight by such committees of clinical trials in India (Cressey, 2012). For example, sometimes doctors whose patients are participating in the trial are part of these review committees. This defeats the purpose of having an independent, unbiased review in addition to the review by the researcher and medical professional (Yee, 2012). In addition to this, the investigators at the head of the clinical trials do not have to be trained in protecting human participants and therefore, there is a lack of ethical insight from the person in charge of the trial ("Investigator Responsibilities," 2013).

Due to this lack of regulation, many clinical trials have resulted in unfortunate events. Recent articles have reported that in 2010, 668 people died during clinical trials in India (Cressey, 2012). Another source reported 1,144 deaths in 2010 and 2011 (Sreelata,

2012), and another gave the number of 2,193 deaths between 2007 and 2011 with compensation given in only 22 of these cases (Silverman, 2013). Due to these complications with clinical research, India is planning to implement new regulations, proposing to register all trials and increase the oversight of the research by ethical review committees (Cressey, 2012). While these actions suggest that India is beginning to accept a more powerful role in the trials, there is a significant amount of debate because these new regulations will increase the cost of the clinical trials limiting the number that can be performed. It is believed that this would slow down advances in medical research (Cressey, 2012). These debates are proof that clinical research has historically been carried out in India due to its low cost, not because the Indians will specifically benefit from the research or because Indians contribute to the research in a unique way. However, it is immoral from a care ethics point of view that the safety and health of vulnerable people have been compromised for the sake money. No matter what the effect on the cost, new regulations should be established to ensure that trials are more fairly performed. It is important to analyze this situation closely because advances in medical research -- which benefit the entire world -- are at stake.

Because clinical research in India provides an easy way to advance medicine, which benefits the entire world including the participants if the trial is successful, some may argue that clinical trials are paternalistic. Since strengthening regulations in India likely would slow down medical advances, some believe this would be more harmful than beneficial for the largest number of people. However, by examining the situation from a care ethics point of view, there is clearly an extremely unbalanced and abusive relationship between clinical researchers and the Indian participants. This uncaring

treatment cannot be justified by any means. Through the lens of care ethics, it is possible to find alternative solutions to this situation that will not result in slower medical advances.

A more equal distribution of volunteers, rather than a concentrated source of participants would allow for medical research to continue at the same pace while being acquired through more ethical and caring practices. This situation is difficult because clinical researchers have trouble acquiring volunteers from educated and developed countries where more people have access to health care and are more informed about the risks involved with clinical trials (Stevens, 2006). For example, even only 3% of cancer patients in developed countries are willing to participate in clinical trials (Kahn, 2006). Reaching the goal of more equally distributed volunteers would require more preliminary tests, such as cell cultures or chemical analyses of the trial drug ("What Happens before Clinical Trials?" 2012). Because these would increase the chance of a successful trial, more volunteers would be willing to participate. Also, the pharmaceutical companies and clinical researchers must more strictly follow the ethical guidelines of clinical research. For example, if research were carried out only in populations that would directly benefit from the research, it would ensure that volunteers would gain benefits from the research and that there would be an equal distribution of the research among many different countries, rather than just one target area. It is also essential for scientific reasons that the medication be tested where it would be used. If many people who would frequently use the medication had already received a different treatment, it would be important to know if this would have an effect on the trial drug. Furthermore, programs educating potential

participants about the trials and more time for the potential participants to think about this information would result in more accurate informed consent from the volunteers.

Since these regulations are already in place but are not always followed, what must be changed is the regulation of the trials. More strict regulations beginning with the preliminary tests and continuing through the phase III clinical trials would generate a higher chance of acquiring diverse volunteers and a higher chance of the clinical trials being successful. In the long run, increased regulations would result in a higher number of new successful medications. The high percentage of successful trials would also increase the amount of successful medications produced. Therefore, increasing regulations and reviews by ethical committees would ultimately increase, or at the very least not decrease, the rate and quality of medical advances.

These solutions would ultimately result in a more equalized relationship between the United States and India, making this situation a more caring one. However, these solutions require that pharmaceutical companies and clinical researchers put aside money and work instead to assist people in areas where help is needed. Only by following this goal of caring for people, rather than a goal of obtaining wealth, can clinical trials become ethical practices for advancing world medical research.

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