Ethical Considerations of Conducting Clinical Research in Developing Countries

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Clinical research in developing countries such as India, Russia and China is becoming very common. Nearly 40% of all clinical trials are now being conducted in third-world countries (18). Pharmaceutical companies are very interested in conducting research in these parts of the world as they offer cost-cutting incentives. With costs of drug development rising higher than $900 million per new chemical entity, companies are looking beyond the US, Europe and Japan for new venues in which to test new drugs (23). This raises important questions about the ethics and oversight of these trials and the protection of participating patients. Research that is sponsored by companies or agencies based in countries with relatively high social and economic development and conducted in countries that are relatively less developed raises many important ethical challenges. Safeguarding the rights and welfare of research participants in developing countries should be a priority (13).

High clinical development costs along with declining drug discovery rates are reducing productivity in the pharmaceutical industry (22). Estimations from industry reflect that the cost of bringing one new molecule to the market costs over $900 million. The European Federation of Pharmaceutical Industries and Associations estimates that, on average, out of 10,000 molecules developed in the lab, only one or two will ever be developed and marketed (4). Many large companies are facing imminent patent expiration of blockbuster drugs that will severely impact their profitability. Increased regulatory scrutiny has also delayed the approval of new drugs. These cost pressures have caused the industry to begin to shift their focus to countries that can minimize the expenses, time, and risk involved in research and development (4).

Research and development costs can potentially be greatly reduced by conducting clinical research in third-world countries because of lower operational expenses, faster patient

enrollment, new regulatory reforms, and a large cadre of English-speaking physicians and nurses (20). Overall costs of conducting clinical research in countries such as India are considerably lower than in the West. Costs per patient, costs per investigator, and the cost of infrastructure and management of trials can be reduced by at least 25% (7). Also cheaper in developing countries such as India are the costs of the many laboratory tests that must be performed. Labor and supplies for these tests are much less expensive. Other cost incentives include regulatory reforms in countries such as India and China that give lower taxes and reduce importation taxes for clinical trial materials (7). Many companies also conduct trials in countries such as China to enable future marketing in the country and widen the commercial market (6).

Also, these countries have very large populations of untreated patients suffering from diseases associated with the developing world, but also with diseases associated with Western culture. E.g., in India, asthma, diabetes, cardiovascular disease, and cancer are prevalent along with the common communicable diseases that affect poorer countries (7). China and Africa also have very large populations of people with both types of diseases very prevalent. Countries in Africa have become very important hosts to pharmaceutical sponsors looking to conduct AIDS trials (13). Huge populations and the wide spectrum of diseases in countries such as these potentially make for quick patient enrollment. These factors can help to reduce the time spent in developing drugs, bringing them to market sooner.

Research conducted in countries such as India is also supported by the large number of English speaking physicians. India has an extensive medical infrastructure and most of India's doctors and nurses have been trained in developed countries (7).

Another reason for conducting research in such countries is encouragement from the FDA to study ethnically diverse populations. FDA requires sponsors of NDAs to submit a summary of safety and efficacy data by demographic subgroup, as well as an analysis of whether modifications to dosages are needed for various demographic subgroups (8). Along with this requirement, FDA has adopted ICH E5 guidelines that recommend a framework for evaluating the impact of ethnic factors on a drug's effect (9). This guidance allows faster approvals of drugs in ICH regions by allowing clinical data from studies conducted in a particular region to be extrapolated to another region using a bridging study to demonstrate safety in various ethnic groups (9). Clinical results from patients in India, China, and other parts of the world may help researchers gain insight into the ways that drugs can affect different ethnicities (18).

It is important to recognize that there are key ethical concerns when clinical research is conducted in developing communities. Issues of informed consent, regulatory oversight, and the use of placebo controls, among others, are of major concern to many involved in foreign clinical research. Clinical drug trials sponsored by developed nations such as the United States and conducted in developing nations in other parts of the world pose unique ethical risks. Taking these potential concerns into consideration before conducting research in developing communities will ensure both the safety of research subjects and faster and more efficient regulatory review and approval of new drugs. Understanding these issues is the first step towards addressing them through ethical guidelines and regulations. A thorough literature review and interviews of several experts in clinical drug research provided many interesting insights into these ethical concerns and some recommendations for the future.

What Are the Key Ethical Issues?

FDA Oversight and Ethics Committee Review:

The ethical aspects of conducting research in developing countries such as India, Russia and China must be considered. While the ethical and regulatory obligations of drug sponsors in the US and Europe are widely understood and considered a routine aspect of doing business, there is a risk that these aspects of conducting clinical research may be overlooked in other parts of the world. A study conducted by the US National Bioethics Advisory Commission to explore the experiences and attitudes of researchers from developing countries found that 25% of responding organizations conducting trials did not undergo local ethics review by any IRB, ethics committee or health ministry (14). Other issues identified with local ethics committee review in developing countries include complex procedural processes mandated by sponsors in the US and ethics committee board members with little or no research experience (11). On the other hand, many times members of Institutional Review Boards in developed countries such as the United States have no experience in the developing world and do not understand the local issues. In many countries, for example, women do not make their own decisions regarding their medical care. Their husbands make decisions for them. This complicates many of the processes and procedures involved in clinical research, especially informed consent. An uninformed ethics committee may recommend procedures that are not culturally suitable, because of a lack of understanding of the local customs (11).

Although data from ex-US trials may be submitted to the FDA in a New Drug Application, FDA oversight of such clinical research is not consistent and the requirements for ethical oversight of foreign studies may not be adequate (17). In a report by Nigerian medical experts, recently

uncovered by the *Washington Post*, Pfizer Inc. allegedly violated international law during a 1996 epidemic by testing an unapproved drug on children with brain infections. Pfizer was found to have given an unapproved drug to children without the consent of the Nigerian government and without obtaining consent from the parents of the sick children. The *Washington Post* article also stated that Pfizer had falsified an ethics committee approval document stating that the study had been approved. Representative Tom Lantos of California described the report's findings as "appalling" and stated that he would introduce a bill requiring U.S. researchers to give the FDA details of tests they plan in developing countries (24).

Studies like these conducted outside the United States not under an Investigational New Drug Application are at issue because they might not come to the attention of the FDA until a drug company later submits the data as part of a filing package seeking approval (17). If the company does not submit the data as part of a New Drug Application, the study may not ever be reviewed by the FDA. Although international ethics guidelines say that all human subject research will be reviewed by an ethics committee, for US sponsored research in developing countries, there may not be a governing body ensuring that this is happening.

The FDA is proposing to revise its regulations on its acceptance of foreign clinical studies not conducted under an IND in support of an NDA. These changes would replace the Declaration of Helsinki as the ethical standard for foreign clinical research with ICH Good Clinical Practices (10). This concerns some ethicists because the GCP guidelines "were not developed transparently and mainly address procedural issues, not overarching ethical ones." (17). The role of the sponsor when it comes to foreign clinical research should be to oversee all aspects of the research and endure that all parties involved are concerned with the best interests of the research subjects. The role of the FDA with respect to clinical drug trials is to enforce regulations put in

place to protect research subjects. Many feel that oversight of foreign clinical research has not been adequate in the past, and these people have many examples to illustrate this.

Informed Consent, Patient Recruitment, and Compensation:

There are specific ethical concerns about patient recruitment practices, informed consent procedures, investigator compensation, and conflicts of interest. Many experts on this subject feel that it is important to recognize that research subjects in developing countries may not be able to give truly informed consent. This could be because of illiteracy, inability to translate documents, or a lack of understanding of clinical research and medical care in general. International guidelines recommend procedures for obtaining informed consent, but these may be difficult to implement in developing countries (25). Can informed consent procedures be adapted to the community where the research is taking place (5)? During an interview with Dr. Uma Sharma, Global Clinical Leader at Pfizer, Inc, this issue was discussed. Dr. Sharma stated that she felt that there are often times when informed consent procedures cannot be fully adapted to developing communities where research is taking place because " a lot is lost in translation." She said, for example, that while it is possible to translate an informed consent document to the local language it may not help the study subjects understand what they are really volunteering to do. She said that it is very hard to explain risks and benefits, placebo controls, and other types of concepts to people that have no exposure the anything like this. Even among literate study subjects in a developed country, there may be a poor understanding of the nature of research (3).

Another important consideration is patient recruitment and the voluntariness of research subjects. Are research subjects in developing countries enrolling into studies because they have no other options for medical care? Dr. Sudhir Borgonha stated in response to this question that people in

developing communities may participate in research because they have no other options for health care. He said that invariably, only those that cannot afford medical care are the ones who participate in trials. The offer of free medical treatment to people who may not have any health care available to them may be coercive. This ties in also to the issues raised above regarding informed consent. There have been several documented studies that have observed consent processes in developing communities that have found that many people from these communities thought it was compulsory to participate even when researchers have followed generally accepted consent procedures. This misconception happens when people think they are receiving treatment rather than participating in research (3). This raises significant concerns of exploitation and coercion (21).

Also important to consider when assessing the ethical aspects of clinical research in developing countries is investigator compensation. Many investigators in developing countries may be paid much more than their base salaries to enroll patients into trials (18). This raises questions of conflicts of interest because, although the investigator should have the best interest of the research participant in mind, he or she may feel pressure to enroll an inappropriate subject into a study because of the money involved. This is also a risk in developed countries, although money paid to clinical researchers by sponsors should not be for personal uses. Because physicians in many countries are thought of as "demi-gods," there is a risk of exploitation of unknowing study participants, stated Dr. Sudhir Borgonha.

Benefit to Research Subjects:

There are also ethical concerns about the question of whether the population from which the research subjects are drawn could ever benefit from the research (19). Many ethicists feel that research subjects should not be drawn from populations that will not be able to benefit from the

research (12). In fact, the Declaration of Helsinki states that "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study." There is also a note that post-trial arrangements or other care must be described in the protocol, so that the ethics committee may consider these arrangements during its review of the study(25). Despite this, there are many examples of recent studies that have been conducted in developing countries where patients would probably never see the approved product because of its high costs. This is especially an issue in African countries that have been conducting AIDS research. In many of the potential countries where the research will be conducted, there is no treatment available to the general population. Despite this, the sponsor is likely to make a profit from the eventual sale of the drugs developed. This disparity is a major ethical issue that must be addressed by the research community, especially as the numbers of people with diseases like HIV/AIDS in developing countries increases (13).

Although most ethicists disapprove of the common practice of testing drugs in developing countries without ensuring access for residents of the community, there is little agreement on how this accessibility can be ensured. (13). This is also an issue in developed countries where many people are not able to gain access to beneficial new medicines because of cost (19). Should the developing communities where research is being conducted be guaranteed a benefit from the outcome of the research? International standards are in place that recommend that research subjects in developing countries be able to gain access to investigational medicines that are proven to be effective. This could be potentially prohibitive to sponsors considering placing their studies in these countries, as it is sometimes difficult to provide drugs to developing communities, not only because of lack of money, but also because of lack of medical infrastructure. For example, the most effective treatment for HIV/AIDS, anti-retroviral

medication, is complicated to administer, requires close monitoring of the patients, and is expensive (13).

Standards of Care/Placebo-Controlled Studies:

Another major ethical concern in clinical research in developing countries is an issue regarding standards of care. An essential ethical condition for conducting a randomized clinical trial is that there is no good reason for thinking that one treatment is better than the other. If there is evidence to support one treatment over another, and the trial is carried out anyway, the investigators would be guilty of knowingly giving one treatment group an inferior treatment. The use of placebo controls in randomized trials is also applied here. It is really only ethical to use placebo controls when there is no known effective treatment (1). However, there have been many studies carried out in developing countries using a placebo control when an effective standard of care did exist. The justification given for this was that since the research participants had no access to the current standard of care, in effect there was no standard of care for these people. Many placebo-controlled AIDS trials have been conducted in African countries using this rationale, despite the fact that anti-retroviral treatments have been established for years as effective treatment (2). Whether research conducted in developing countries can be held to different standards than research conducted in developed countries is highly debated. The Declaration of Helsinki was revised in 2000 to include language stating that all trial participants worldwide are entitled to the best standard of care, not the local one, but many developed countries have argued that there may be good reasons for allowing a different level of care for research in developing countries (16). The justification given for carrying out such research is that a placebo-controlled study is the fastest, most efficient way to obtain unambiguous data, and that someday, this will benefit the developing world (1). The outcome of this debate will have very important ethical implications for research subjects in developing countries.

Another of the questions raised is whether researchers should be required to provide better care for their subjects than what is generally available in the community. International guidelines say that the goals of research should always be secondary to the well-being and safety of the participants (1). If medical resources are available to study subjects in developing communities because research is being conducted, the investigators should be obligated to provide the best care available. According to Marcia Angell, a prominent ethicist and critic of pharmaceutical researchers, these ethical codes have been put in place because there is a "strong temptation to subordinate the subjects' welfare to the objectives of the study." (1) She feels that many times human subjects are treated as a "means to an end." (1) This certainly appears to have been the case in many recent studies that have jeopardized the health of study subjects for the purposes of research, for example, the recent disclosure of the 1996 Pfizer trial in Nigeria.

The textbook example of unethical research and the standards of care debate is the Tuskegee Syphilis Study. In this study, 412 destitute African American men with syphilis were followed for 40 years to determine the natural outcome of the disease. Even when treatment for syphilis became available, the men were not treated. The subjects were denied the best known treatment to further the goals of the research (15). The justification given here again was that these people probably would not have been treated anyway, so the study was merely mimicking what would have happened if there were no study. The risk here that relates to current medical research is that accepting this justification could result in widespread exploitation of vulnerable populations in developing nations for the purposes of carrying out research that could not be conducted in the developed world (1).

Q & A with Industry Experts:

As part of this project, a list of questions was developed to collect information from people currently working in clinical research about their knowledge and experience with this topic. Questionnaires were sent to 14 people who are currently working in drug development and clinical research and who have extensive experience conducting clinical trials. The following people shared their experiences with clinical research in developing countries:

Dr. Richard Day, Professor of Clinical Pharmacology and Director of Clinical Pharmacology and Toxicology, UNSW and St. Vincent's Hospital, Sydney

Dr. Clifford Siporin, Founder, Greystone Consulting

Dr. Uma Sharma, Global Clinical Leader, Pain, Pfizer

Dr. Sudhir Borgonha, CEO, ClinTest International

Dr. Camila Fowst, Global Clinical Leader, Oncology, Pfizer

Following are the questions asked and a summary of the answers given:

1) What is your experience with conducting trials in developing countries?

   All five people have extensive experience in clinical research. In addition, all of the people interviewed have conducted US sponsored clinical trials in developing countries such as India and China. Dr. Uma Sharma and Dr. Sudhir Borgonha are from India and relayed some of their experiences with the health care system in that country.

2) From your experience, what oversight is provided by the US FDA for clinical research in developing countries?

   The answers received for this question varied. Four out of five people felt that FDA oversight of foreign drug research is adequate. Dr. Day and Dr. Sharma both

brought up the fact that the FDA has the authority to inspect study sites in other countries. Dr. Sharma also mentioned that the FDA an inspect sites that are participating in research not conducted under an Investigational New Drug Application, but this is usually based on the amount of data coming in from other countries. Dr. Siporin stated that he has actually had study sites that he was responsible for in India inspected by the FDA.

Dr. Borgonha, on the other hand, felt that the FDA does not play a very active role. He stated, though, that he thinks this will be changing as the amount of research conducted in developing countries increases. According to him, the US FDA and other regulatory agencies will be providing more oversight in the future.

3) From your experience, what oversight measures are instituted by sponsors concerning clinical research in developing countries?

For this question, all five people interviewed felt that the majority of sponsors institute the same ethical standards and oversight measures in developing countries that they do in developed countries. Dr. Siporin and Dr. Fowst stated that the oversight measures and standards for US sponsored research in developing countries are the same as they would be in developed countries as ICH guidelines apply worldwide. US sponsores rely on CROs and monitors that are actually in the country to oversee the protection of research subjects, according to Drs. Sharma and Borgonha. When asked whether she has participated in discussions about potential ethical concerns with the FDA while discussing plans for research in foreign countries, Dr. Sharma said no, that this is really up to the sponsors.

4) Is special consideration given because of the risk of ethical issues, or is the oversight similar to what it would be for developed countries? Please explain.

Dr. Day felt that this would probably depend on the country and the type of study and drug to be researched. He said that he suspected that for sponsors and regulatory agencies this is a "risk-based" and "experience informed" approach. Four of five people questioned on this topic felt that sponsors implement oversight measures that are similar to those of developed countries, even though many of the ethical issues are different.

5) Have you been involved with clinical research conducted in developing countries where there were potential ethical concerns that needed to be addressed before the research took place? What were they? What was done to address them?

Drs. Sharma and Borgonha felt that one of the biggest issues is informed consent. According to Dr. Sharma, " a lot is lost in translation," and explanations of risks and benefits, study procedures, and the use of placebo controls may not have a lot of meaning to people who are not familiar with medical treatment. Both Dr. Sharma and Dr. Borgonha brought up the high illiteracy rate in countries such as India. Dr. Sharma said that sponsors of clinical trials can use measures such as third-party witnesses to help ensure that study subjects understand the study and are giving informed consent, but that this is hard to implement and oversee all of the time. She said that there have been cases of informed consent discussions where the third-party witness has not been physically present and has just listened over the phone. Dr. Borgonha said that it is difficult to ensure that truly *informed* consent is being obtained due to the following reasons:

a. “Over 90% don’t speak English
b. There are over 30 odd official languages
c. Each state has its own language
d. Doctors are still demi-gods in developing countries-so their word is always taken as good.”

Interestingly, Dr. Siporin stated that although he has conducted clinical trials in developing countries, he has always ensured that people who cannot read are not enrolled into the trials.

Another issues that was raised as important was patient compensation. It is extremely difficult to ensure that study subjects are not being coerced by the amount of compensation offered for their participation in a trial. Even the offer of free medical care may be coercive to some, Dr. Siporin said. He also said that his company puts a lot of thought into the amount of compensation that should be offered to study subjects, if any. They consult with local ethics committees who have a better understanding of the community than a central ethics committee that is often in another country. Dr. Borgonha felt that this is also an issue because it is often the case that only those who cannot afford even basic medical care agree to participate in trials.

Dr. Sharma also raised another very interesting issue. She noted that there are trends in research in developing countries where there is a lower incidence of adverse events and withdrawals from research compared to subjects in other countries. She felt that this is due to the high status that physicians have and the reluctance that patients have to complain. She said that one way to counterbalance this is to design studies to collect hard endpoints versus soft endpoints. For

example, hard endpoints such as blood pressure and tumor size are objective measurements whereas the collection of endpoints like pain and nausea is heavily dependant on the subject. Collecting hard endpoints puts the study subject at less risk, according to Dr. Sharma, because there is less of a chance that a subject will stay enrolled in a trial even though they are experiencing adverse events. The study doctor is not dependant on patient reported measures to determine how the subject is doing.

The intention of this project was to explore the key ethical issues to be considered when US sponsors conduct research in developing countries through and to collect thoughts and opinions from experts in the field. Since the drug development industry is looking more and more toward outsourcing clinical trials to regions where they can be conducted faster and cheaper, it is imperative that these ethical issues are examined. Many of the responses from those that answered the questionnaire indicated that they were not aware of many of these issues, or at least did not acknowledge their relevance. More researchers from the developed world need to be informed of these issues. For several issues, however, there are no reasonable means of resolution, as the issues at stake are subjective in nature. It is up to the international research community to determine the ultimate outcome of these very important questions.

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