

Clinical Drug Testing In The Developing World: Ethical and policy implications

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Clinical drug testing is an unavoidable aspect of drug development and approval. Although most therapeutic drugs are developed by Northern scientists and pharmaceutical companies, clinical drug testing may still be conducted in developing nations for a variety of reasons, including the availability of adequate numbers of potential patients, the low cost of conducting the trials and the fact that some diseases, such as tropical diseases (Bilharzias, leishmaniasis and sleeping sickness), are of greater public health importance in developing countries than in the developed world.

Regardless of where clinical drug testing is conducted, it is important to always give due consideration to internationally accepted codes of practice, such as the Helsinki Declaration, the Council for Inter-

national Organizations for Medical Sciences (CIOMS) and the UN's Universal Declaration on Human Rights.¹⁻³ This paper focuses specifically on the ethical and policy implications regarding the conduct of clinical drug trials by international companies or research groups in developing nations. The terms "Northern" and "developed" nations have been used interchangeably, as have been the terms "Southern" and "developing" nations.

Ethics of Research

Ezekiel Emanuel, et al. have ably discussed what makes research trials ethical.⁴ For clinical drug trials to be performed ethically in Southern countries,

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the following should be demonstrated: social and scientific value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review of the research protocol and implementation and informed consent obtained from research participants.

Informed Consent by Research Subjects

Obtaining informed consent from the potential research participant is a basic requirement for the conduct of any clinical drug trial.^{5,6} For consent to be informed and ethical, four conditions must be fulfilled: 1) having received relevant and adequate information, 2) understanding that the process is within a clinical drug trial, 3) being able to choose whether to participate or not participate without compromising the standard of care one is normally expected to have and, 4) being legally competent to make an informed, voluntary choice by the person who is giving consent. If any of these four requirements is not met, it is difficult to suggest that informed consent has been obtained.

The actual practice of obtaining informed consent may differ from community to community. Ideally, a written informed consent is obtained from the research participant. However, in many regions of developing countries where literacy levels are low, this is not always possible. This should not absolve the researcher from his or her responsibility to ensure that informed consent is obtained. Verbal, documented consent, attested to with a thumbprint, may be the solution in the many areas of developing countries

without viable alternatives.

The practice suggested above has its own challenges, however. We are aware of situations, not in clinical drug trials, but in surgical operations, where illiterate patients have been asked to thumbprint documents outlining procedures that have not been fully explained to them. Institutional Review Boards (IRBs) should be able to verify the provision of consent in all situations, but doing so in such situations as described above is rather imperative.

In some developing countries, community approval may also be required if any drug trials are to be conducted. Community assent can be obtained through chiefs, heads of a group of households and others of similar responsibility and authority. However, the researcher should realize that community assent is not a substitute for individual informed consent, which must still be obtained.

There are several issues that need to be considered when gauging the competence of an individual to provide informed consent. Often, competence to participate in a clinical drug trial is based on meeting age, mental health and informed consent requirements. However, all of these elements have limitations. We do not live in a perfect world, and most tools that are developed to assess whether individuals have demonstrated informed consent will need modification, if not outright rejection, with the passage of time and the development of new insights.

Consider for instance the criterion of age: that one must be an adult to give informed consent. The age at which one legally becomes an adult is usually between 18 and 21 years. This age of majority was likely arbitrarily chosen as a surrogate age

at which an individual can legally marry or vote. Are the competencies required to participate in selection of political leaders the same as those that may be required to accept or refuse participation in a trial? The age constraint is a factor that may either facilitate or impede the goal of determining competency. For instance, consider an uneducated and illiterate 30 year-old man and a 17 year-old medical student. If age alone is taken into consideration, the 17 year-old medical student may be ineligible to participate in a drug trial and yet may have a better understanding of the biological aspects of the clinical trial. On the other hand, the 30 year-old man may have a more complete view of the world because of his maturity and life experience and, therefore, may be better equipped to make crucial life choices than the younger medical student. From the example above, it is clear to us that any suggested tool for ethical evaluation will have limitations, but this realization should not dissuade us from refining the available tools.

The traditional informed consent form used by many Northern researchers is usually a complicated document that not only is difficult to translate into local languages but that also seems to be aimed at protecting the researcher rather than informing the research participant. The importance of informed consent must be stressed to prevent the participants and their communities from misunderstanding the clinical research being conducted.

Local Approaches to Informed Consent

Mfutso-Bengo and Taylor suggested that

while ethical principles are universal, the application of these principles may differ depending on prevailing social, cultural and other factors.⁷ Mfutso-Bengo and Taylor suggest that the following also need to receive due consideration when informed consent is being obtained: 1) appropriate wording and speech that clearly present relevant information to the potential research participant, 2) appropriate timing to minimize coercion and to enable the participant to be in “the right frame of mind,” 3) appropriate setting or premises to maintain the privacy of the potential participant and 4) presence of and interaction with a trusted person on the research team.

Misunderstanding Drug Trials

It has been reported that research subjects may misunderstand the purpose of clinical trials.⁸ We would like to discuss a category of misunderstandings known as therapeutic misconceptions, i.e., therapeutic misconception, therapeutic misestimation and therapeutic optimism.⁸ These concepts are described further below. We are alerting researchers, IRBs, communities and research funders to the existence of these misunderstandings so that they can institute preventative measures. In addition, it is important to note that patients are not the only group that may misunderstand the purpose of research. Joffe and Weeks reported in a study that clinical oncologists believed that clinical trials were aimed at benefiting individual patients.⁹

Therapeutic Misconception

The concept of therapeutic misconception was first described by Appelbaum, et al.¹⁰ Therapeutic misconception occurs when the research participant believes that “every aspect of the research project is designed to help him/her directly.” While benefit to an individual may be possible in a clinical trial, the main purpose of a research project is to generate knowledge that can be generalized to a larger population. Participants may not always understand this fact, as it may not be well-explained to them. However, if a research participant thinks that the purpose of the research is to maximize her or his own benefit, tension may arise as the patient’s basis of choosing to participate in the research is based on a wrong understanding of the actual situation. It is possible had he or she known that the primary purpose of the treatment was to generate general knowledge useful for the future, the patient may not have consented to participate in the trial. In this case, the basis of the participant’s decision to be involved in the study is the perception that the trial is for personal benefit, as in routine clinical care, and the participant cannot be said to have given informed consent.

Therapeutic Misunderstanding

Therapeutic misunderstanding occurs when the research participant overestimates the probability that he or she will benefit from the research while underestimating the risk inherent in the study. Again, in

situations where this occurs, the individual participant’s autonomy is compromised, as his or her decision to participate may not be well-informed. One of the questions we need to consider is how research participants understand and use the concept of probability to make reasonable decisions. Depending on how information is presented, participants may understand the issues differently. For instance, Horng and Grady suggest that patients may interpret probabilities differently when they are presented as odds as opposed to frequencies.⁸

Therapeutic Optimism

Therapeutic optimism occurs when research participants think that the benefits that may be possible in research trials will be directed to them. Therapeutic optimism may be tolerated where the patient does not have the other forms of misunderstanding as presented above, i.e. the study subjects understands that he or she is participating in a clinical drug trial and does not think that the purpose of the treatment is for current individual benefit, but he or she just has a positive attitude toward the treatment.⁸

Neglected Diseases

The World Health Organization and its partners have identified some illnesses, mostly affecting developing nations, that have been described as “neglected diseases.” These include conditions such as African Trypanosomiasis (sleeping), leishmaniasis and schistosomiasis (bilharzias). These diseases create enormous economic costs

and contribute greatly to human suffering in the affected countries. It makes sense, therefore, that clinical drug trials targeting these diseases should be conducted in the countries affected. However, in practice, this does not always occur. There are situations where clinical specimens are collected from research participants and analyzed in Northern laboratories. This is unacceptable, as this practice facilitates and continues developing nations' dependence on the North. Instead, we suggest that virtually all specimen analysis for these so-called neglected diseases should be conducted in the developing nations. This can only be achieved through transfer of skills and technology. Funding agencies can ensure that researchers in the North are always incorporating capacity development in their trials in the developing nations.

North-South Collaboration

One of the most important aspects of clinical drug trials conducted in developing countries is the requirement that there is capacity building of skills and technology in the developing country where clinical drug trials are being conducted. This has been the case in some North-South collaborative initiatives. It should no longer be acceptable to have reasonably critical equipment or skills, such as polymerase chain reaction (PCR) machines and CD4 count determination (a test aimed at determining the level of immune status, especially useful in the care of HIV infected persons), only in the hands of Northern collaborators without any transfer of expertise to developing country scientists when research studies requiring these tests

have been conducted. This transfer of skills to Southern scientists can take the form of mentorship, sponsorship for training or apprenticeship.

Risk-Benefit Analysis

A thorough risk-benefit analysis is an important aspect of all clinical drug trials. Researchers should always endeavor to minimize risk to individual research participants, society, the community and the environment. If the potential risks to individuals and society from participating in the trial outweigh the benefits, it is unethical to conduct the trial.¹⁻³

Conflict Resolution

Clinical trials conducted in developing countries by Northern-based researchers almost always face challenges regarding differences in the cultural, social and moral backgrounds of the researchers and the subject community. Conflicts and disagreements on the interpretation or implementation of ethical principles are inevitable. Mfutso-Bengo and Taylor have argued that "...in situations where the application of a fundamental ethical issue is contentious, the final decision should fall within the jurisdiction of the local ethics committee (assuming it is properly constituted and can act independently)."⁷ However, Muula disagrees and argues that while it may be preferable that a developing country's local IRB decision should have precedence over a remote (for instance US-based) IRB, the final decision should really be based upon a case by case consideration. What if the

local IRB errs in matters of principle? Should it be always be given the benefit of doubt?

The case study that Mfutso-Bengo and Taylor present to support their argument involved an autopsy on childhood malaria victims. The purpose of the study was to determine the association between abnormalities of the retina and concomitant histological abnormalities. Parents or guardians whose child had died in a research ward from malaria were invited to allow an autopsy to be carried out on the dead child. As part of the study, the children's eyes were to be removed and eye prostheses fitted in place. The parents and guardians were not to be told that the eyes would be removed and replaced by eye prostheses. The local IRB, suggesting that disclosure would do more harm than good and that recruitment of participants might be hampered, did not have a problem with the non-disclosure to parents of the removal of eyes. However, the US-based IRB with which one of the research staff was affiliated argued that non-disclosure was paternalistic and compromised informed consent. The matter was resolved through negotiations between the two IRBs involved. It was agreed that disclosure would have been perceived as culturally inappropriate as doing so would be insensitive to the family that had just been bereaved, thereby causing "psychological harm." Even now, we disagree between ourselves. The purpose of the presentation of this case study is not so much to expose the fact that we hold different views, but to show that individual values and experiences that influence decision-making are not homogeneous. The composition of IRBs may also matter; what is acceptable to one local IRB under

certain leadership and membership might not be acceptable in the same country under different leadership and membership.

What Happens When Research Is Over

The issue of post-trial benefits was a matter of intense discussion at the 6th Global Forum for Research Bioethics held in March 2005 in Malawi. One of the conclusions was that post trial activities should include the immediate dissemination of research findings, not only to funding institutions and Northern journals but also to communities and researchers in developing countries. Many researchers in developing countries have little access to Northern journals for a variety of reasons, including lack of money to subscribe to the publications. Therefore, research results from developing countries published in Northern journals are essentially inaccessible to researchers in developing countries.¹¹ This must be corrected.


It has been argued that trials conducted in developing countries where the technology or drug tested may not become widely available are unethical. Theoretically, this is reasonable. However, the story of anti-retroviral (ARVs) drugs may provide us with a different perspective. For some time, it was inconceivable that ARVs would be accessible to the majority of Africans due to prohibitive cost of the therapy. However, this has changed, and ARVs are increasingly becoming a reality in Africa, due to multiple local and international initiatives.¹²

Research Governance

At the Global Forum for Bioethics, the issue of post-trial benefits was raised. We propose a way to forward the idea of prior agreement among stakeholders (community, IRBs, research funders, department of health, industry, researchers) based on a framework of distribution of research benefits. By this we mean, through observance of transparency, being accountable and responsible towards the other stakeholders. In a spirit of inclusiveness and fairness, there should be prior agreement between the researcher, the funding institutions and the subject community as to what is likely to be provided when the clinical drug trial is successful. Efforts must be made to ensure this process avoids inducing the research participants into accepting to participate when they would not have otherwise done so. We refer to this process as research governance. Not every clinical trial will warrant the same level of engagement of all stakeholders. The level of engagement should depend on the degree of potential risks and benefits. If the risks or benefits are high, engagement should also be high. The process of negotiations that will lead to prior agreement ought to be guided by the following principles: 1) transparency, 2) accountability, 3) responsibility and 4) engagement.

We suggest that employing the concept of research governance is one way of solving the problem of distribution of benefits once the trial is over. This should be achieved through dialogues about ethics between all stakeholders in search of common good, free of exploitation.

Conclusion

Drug trials in developing countries by Northern researchers are an inevitable aspect of globalization, especially when treatments regarding diseases rare in Northern countries are concerned. The diversity in cultural, social and moral backgrounds between the researchers and study participants pose particular challenges. We, however, affirm that the principles of international bioethics must always be respected, while being cognizant of the local application of such principles. Funding institutions should be willing to support the engagement of researchers and subject community in dialogue in order to determine a priori what may be community benefits once the clinical drug trials are over. 

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References

1. Council for International Organizations of Medical Sciences. *International Ethics Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland, CIOMS; 1998
2. The Nuremberg Code. *Journal of the American Medical Association* 276 No (1996), 1691
3. World Medical Association. Declaration of Helsinki . *Journal of the American Medical Association* 277 No (1997), 925-926
4. E.J. Emanuel, D.Wendler , C. Grady. What makes clinical research ethical. *Journal of the American Medical Association* 283 No 20 (2000), 2701-11

5. R.R. Faden and T.L. Beauchamp. History and Theory of Informed Consent. New York: Oxford University Press, 1986: 235-273
6. S. Joffe , E.F.Cook ,P.D. Cleary, J.W. Clark, J.C. Weeks Quality of informed consent in cancer clinical trials: a cross sectional survet. Lancet 368 No 9295, (2001), 1772-77
7. J.M. Mfutso-Bengo, T.E. Taylor. TRENDS in Parasitology 18, no 5 (2001), 231-234
8. S. Horng, C. Grady. Misunderstanding in clinical research. Distinguishing Therapeutic Misconception, Therapeutic Misestimation and Therapeutic Optimism. IRB: Ethics and Human Research 25 No 1 (2003): 11-16
9. S. Joffe and J.C. Weeks. Views on American oncologists about the purposes of clinical trials. Journal of the National Cancer Institute 94 No. 24, 1847-53
10. Appelbaum, L.H. Roth, C.W. Lidz, P. Benson, W. Winsdale. False hopes and best data. Consent to research and the therapeutic misconception. Hastings Center Report 12 no 2 (1987), 20-24
11. A.S. Muula. Is there any solution to the "brain drain" of health professionals and knowledge from Africa. Croatian Medical Journal 46 No 1 (2005), 21-9
12. A.S. Muula, H. Misiri, Y. Chimalizeni, D. Mpando, C. Phiri , A. Nyaka .Access to continued professional education among health workers in Blantyre, Malawi. African Health Sciences 4 No 3 (2004), 182-4