Healthcare Research in Developing Countries: Ethical Issues

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Abstract

Background: In recent years, Western organizations and companies have been increasingly using countries of the developing world as places of clinical trials. The involvement of human subjects in healthcare research evokes ethical concerns, especially when their culture is different and their socio-economic status is lower than the Western standards.
Method and Material: A systematic analysis of documents related to the ethics of clinical trials involving human subjects, with particular emphasis on the developing world.
Result: The most important areas of concern include the issue of informed consent, the subjects' compensation, their standard of care, the presence of Research Ethics Committees in developing countries, and the question of what happens after research is over.
Conclusion: Even though many ethical issues are far from clear, and the risk of human subjects' exploitation is always possible, Western-funded research in developing countries should continue; potential benefits outnumber the risks.

Keywords : research ethics, developing countries, human subjects

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Introduction

Bioethics is about ethical issues in the field of health care; it is the discipline which aims at ensuring that health care professionals, researchers, policy-makers, and even lawyers who deal with health care law, exercise their duties in the most just and ethically acceptable way. Consensus in ethical issues is not always possible, but at least there is an effort taking place; some basic ethical principles are widely recognized, and scholars all over the world try their best to provide us with guidelines and declarations on a variety of issues, such as respect for the patient's autonomy, abortion and euthanasia, reproductive technologies and cloning, just allocation of resources, clinical ethics, and, of course, the issue of clinical trials involving animals, and, more importantly, human subjects. This paper examines the issue of healthcare research involving human subjects, with a focus on trials taking place in developing countries, either by organizations and companies of the industrialized world alone, or in collaboration with local researchers. This obviously raises even more ethical issues, as the position of human subjects in the developing world is more delicate in many ways, as it shall be shown in what follows.

Historical Context

History abounds with examples of people with power using humans as guinea pigs. King Mithridates VI of Pontus, afraid of being poisoned, discovered one of the most famous antidotes in antiquity, by experimenting with different ingredients and trying them out on condemned prisoners.[1] When King Louis XIV of France was sick, they called people with similar symptoms to a minister's house where the royal surgeon could practice on them; many of these died, but in the end the surgeon gained valuable experience and he was able to operate on the king with great success.[2] In the Tuskegee experiment, the US authorities measured the progress of syphilis in African-American sharecroppers without telling them they had the disease or adequately treating it, while it recently came to light that the US government medical researchers infected almost 700 people in Guatemala with two sexually transmitted diseases, more than 60 years ago; the patients - prisoners and people suffering mental health problems - were unaware they were being experimented upon. [3,4] However, the most famous case is the one of Nazi human experimentation, which took place in concentration camps during World War II, and involved malaria, sulfonamide, mustard gas, and freezing experiments. After the war, these crimes were tried at what became known as *The Doctors' Trial* and this led to the development of the *Nuremberg Code of Medical Ethics* in 1949, the first generally accepted document governing research with human subjects. This code, in turn, led to the development of the *Declaration of Helsinki* in 1964, and its subsequent revisions – with the 6th Revision being the most recent one, in 2008.

Relevant Regulations

The Declaration of Helsinki issued by the World Medical Association, is not by itself a legally binding instrument in international law, but it has been used as guidance for many national statutes and regulations.[5] In addition, it is morally binding on physicians, and that obligation overrides any national or local laws and regulations (Article 9). Its basic principles include: respect for the individual (Article 8); that the subject has the right to make informed decisions regarding participation in research (Articles 20-22); the subject's welfare must always take precedence over the interests of science and society (Article 5); that research should have a reasonable likelihood of benefit to the population studied (Article 19), and it should be supervised by an independent ethics committee (Article 13); and there are also several other provisions, including surrogate consent for minors. Other international documents of interest include

pp: 243-250
E-ISSN:1791-809X www.hsj.gr

the ethical guidelines issued by the Council for International Organizations of Medical Sciences (CIOMS), a non-governmental organization that works in collaboration with the World Health Organization (WHO); and the Clinical Trials Directive (2001/20/EC) of the European Parliament and of the Council, to which all member states of the European Union adhere. Furthermore, there exist other documents, national laws, declarations, and international guidelines on human experimentation, but there is no need to mention all of them, as they are based on the same principles, and essentially ask for the same measures.[6,7]

So, when it comes to human subjects, clinical trials seem to be regulated very effectively. However, the effectiveness of these regulations has always been contested, and this is why the debate is still on and further revisions of existing documents are to be expected. The enforcement of regulations in practice is much more difficult than their theoretical formation. Sometimes, there are even ways of by-passing laws and declarations, if these are inconvenient, and treat human subjects in a way which comes at odds with all the above mentioned statements and guidelines. One can naturally assume that this is easier to take place in the developing world; these countries have so many problems, that it is often difficult to pay particular attention to the issue of research ethics and clinical trials. In addition, a parallel approach to the whole issue may be necessary, considering the radically different cultural backgrounds and socio-economic statuses of people in developing countries, compared to those of the industrialized world. Therefore, the ethics of medical research in developing countries has been a much debated topic, which requires special attention. It is worth mentioning two more related documents: first, the Opinion of the European Group on Ethics in Science and New Technologies to the European Commission, entitled "Ethical Aspects of Clinical Research in Developing Countries" which provides help to the Commission in the exercise of its responsibility regarding the implementation of EU-funded research activities in countries which culturally or economically differ from the West European context; and, second, a report by the Nuffield Council on Bioethics, entitled "The ethics of research related to healthcare in developing countries" and its follow-up discussion paper, which specifically consider externally-sponsored research as it affects those in developing countries. [8-10]

Reasons behind the expansion of healthcare research in developing countries

But why is it that Western pharmaceutical companies decide to conduct some of their research in developing countries, thus making it necessary to provide ethical protection to their subjects? One could think that it allows them to do whatever they want without consequences, but this is a gross oversimplification, largely induced by recent media hype on some real-life cases, followed by public hype on fictional ones. For instance, John Le Carré's novel *The Constant Gardener* presents in a clear way some of the problems with clinical trials in developing countries.[11] Its basic assumption is that 'no drug company does something for nothing.' Drug companies have millions to spend on Public Relations, and this is the reason why many unethical or unlawful procedures remain unknown. The author mentions some minor problems, such as that branded Western drugs are sold in Africa at five times the price, that corrupted officials make profit out of drugs which companies donate, or that these free drugs are well beyond their sell-by date (companies donate them for tax exemption purposes).[12] Then he describes a really disturbing case of clinical trials, where human subjects were not informed that they were testing a new drug; and if they did not give consent, they would not get any medical care. Also, some of them died but the researchers excluded these cases from their results, as it would cost them time and money to repeat the procedures and develop a safer drug – it was easier and cheaper to

pp: 243-250
E-ISSN:1791-809X www.hsj.gr

bribe some people, and kill those who expressed concerns.

Whether completely or partly fictional (the author had claimed that reality is much worse than what his novel described), this is certainly an extreme case, fit to become an international best-seller. However, it is not common for Western organizations and pharmaceutical companies to engage in such profit-hunting extremities, since they have very good and compelling reasons for expanding their research activities in developing countries. First of all, they often collaborate with local researchers. Recently some African countries have started working on ways to develop new drugs for their population. However, lack of resources and weak infrastructure mean that many researchers in developing countries have very limited capacity to conduct their own clinical research. They therefore often undertake research in partnership with groups from developed countries. This means that local researchers, and consequently, their countries, benefit from an opportunity to use foreign scientific knowledge and economic resources, and further develop their own infrastructures. This is why research in developing countries may often be supported by local governments, as it is clearly a way of educating and training local health care professionals. Also, a significant obstacle for Western companies conducting research on HIV or TB drugs, or on tropical diseases, is the shortage of people who take part in Western countries, since the incidence of these diseases is not very high.[13] They are much more common in developing countries however, so it makes perfect sense to take their research there, where appropriate participants abound, even though this procedure costs extra money.[14] Besides, since these diseases constitute a big problem mainly for the developing world, any researches aiming at eliminating them are of primary interest to the developing countries where they take place.

Finally, let us not overlook the possibility of altruistic motives; industrialized countries may fund research in developing countries, not only for the sake of the advantages that this expansion entails, but also out of pure willingness to offer something to the less fortunate. The honesty of these altruistic motives is often compromised by bad publicity. Apart from fictional negative cases, such as the one described above by John Le Carré, there have been real ones, such as the legal case against Pfizer, which started back in 1996; Pfizer had conducted clinical trials to test an antibiotic against meningitis on 200 children in Nigeria, without obtaining the subjects' proper consent. Eleven children died and others were blinded, paralysed or brain-damaged (Pfizer denies all allegations); their relatives and the Nigerian government sued, and in 2009 a settlement was achieved between the company and the Nigerian government. In addition, in 2010 the US Supreme Court has given Nigerian families the green light to sue Pfizer over the use of the new antibiotic on their children.[15] This is certainly interesting, for it implies that Western multinational companies may not engage in unethical or unlawful practices in developing countries, without facing any consequences; but it is also a notorious procedure, which makes the public skeptical about the true motives and good faith of Western investors. However, it would be unjust to disregard the West's genuinely good intentions based on such incidents.

Ethical concerns on developing countries

To be sure, good intentions are never enough on their own. In 2006, William Easterly, former World Bank economist, published a book where he argued that the Western countries' efforts to aid developing countries of the Third World have done little good, and much ill. He estimates that the West has spent $2.3 trillion on foreign aid over the last five decades, but still, it has not managed to get twelve-cent medicines to children to prevent half of all malaria deaths.[16] One of the reasons for this tragedy is that Western policy makers often fail to take into account some major differences between the functioning of developed and developing countries. A plan may look feasible when it is conceived and designed in

some office by experts who have never faced the real circumstances of a developing country, but it does not have much chance of success in practice. Some of the most important factors include cultural and educational differences, lack of proper evidence and statistics, unexpected armed conflicts, corruption, and disrespect for laws, regulations, human rights, or the value of human life itself. Likewise, the principles of Helsinki or other guidelines make sense to Western researchers and research subjects, but people in developing countries may not understand their importance. Thus, the inequalities and differences that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out. The Nuffield Council on Bioethics has identified the most important areas of concern, which are briefly discussed below.[9]

1) Informed consent

Informed consent has been one of the cornerstones of modern bioethics, but it tends to lose its true meaning when put in the context of a developing country. In Western societies, it means that one has to fully understand the nature of the procedure which is about to take place, have the opportunity to have one's questions answered, and agree to it without any kind of coercion being used. This is difficult to happen in, for example, a Sub-Saharan African country. Consent forms often appear to be designed to protect researchers and their sponsors rather than participants. The subject may not be able to understand what the purpose of the experiments is, or what the disease itself is all about. He or she may be illiterate, which means that one has to explain verbally, in full, the conditions which are usually written on paper; then he or she won't be able to sign the appropriate documents, which means that verbal consent has to be used, formally documented and witnessed. Besides, a signature may appear suspicious: for example, in Malawi, trial participants were often concerned that signing may entail unforeseen obligations, such as tax liabilities or trouble with the police.[10] Also, there may be problems with the translation; many languages will not have corresponding terms for words such as 'placebo' and particular care is needed if the research is to be explained successfully.[17] Finally, one needs to consider other cultural differences: for example, it is not unusual for men to make all the decisions in an African family, which means that women may not be able to give an informed consent without the husband's approval. All these issues have to be carefully considered.

2) Compensation

The Council for International Organizations of Medical Sciences (CIOMS) recommends that payments to research participants, either in money or in kind, 'should not be so large as to persuade them to take undue risks or volunteer against their better judgment'.[6] Where health care facilities are lacking, the availability of treatment during and after a trial might also count as an inducement. The point at which inducements become excessive was not always clear. In many developing countries, $5 for loss of earnings or for travel costs could be a substantial incentive for individuals to participate. In general, incentives to participate in research, such as guaranteed access to otherwise unavailable health care, and modest financial recompense for time and travel, are appropriate and should not be viewed as constituting coercion.

3) Standard of care

With regard to the provision of care, most of the guidance does not address the obligations of sponsors. Some argue that when research is externally sponsored, participants in developing countries should receive the same standard of care and treatment as participants would receive if the research was conducted in the country of those sponsoring the research; any other position could lead to the exploitation of people in developing countries.[18] Others claim that a requirement for a universal standard (that is, the best treatment available anywhere in the world, wherever

pp: 243-250
E-ISSN:1791-809X www.hsj.gr

the research is conducted) could prevent research that has the potential to benefit people in developing countries from being undertaken.[9] Requiring sponsors to meet costs of a universal standard of care nay have far reaching implications, some of which may be detrimental to public health. Therefore, this is another complicated issue which remains far from settled; for the time being, a "double standard" can still be justifiably used.[14]

4) Research Ethics Committees

According to WHO, 'countries, institutions, and communities should strive to develop Ethics Committees and ethical review systems that ensure the broadest possible coverage of protection for potential research participants and contribute to the highest attainable quality in the science and ethics of biomedical research. States should promote, as appropriate, the establishment of research ethics committees that are independent, multidisciplinary, multi-sectoral, and pluralistic in nature. Research ethics committees require administrative and financial support'.[19] These committees are important, as their role is to ensure that all the proper procedures take place, without any legal or ethical deviations. They have the task to evaluate research proposals with special attention to risk/benefit ratios, the adequacy of information provided for subjects, and the protection of freedom within the consent process; they also ensure that subjects can withdraw without prejudice to care, and they educate researchers and the community in understanding the ethics of research. However, RECs are quite often absent, ineffective or under-resourced in many countries.[10] Much more need to be done about this.

5) What happens after research is over?

Information gained from clinical trials conducted efficiently and expeditiously in developing countries may allow early registration of drugs in developed countries, thus considerably enhancing profits. It does not seem unreasonable to expect that such profits should also benefit the citizens of developing countries in which the research was undertaken, including the provision of proven treatments following completion of the trials. So, what happens once research is over? International guidance does not address this question either.[20] Many people would like to see participants given guaranteed access to interventions shown to be successful, but this is rarely a simple matter. Providing access will depend upon several factors including the existence of alternatives, the relative burden of disease, and the costs of supplying treatment. For instance, in the case of HIV/AIDS therapy, a research participant should not discontinue the use of a drug proven successful after research is over; such an interruption could easily result in the emergence of resistant strains of HIV, and this should always be an important consideration, both for the developing, and for the industrialized world.[21,22] Still, HIV/AIDS therapy is rather expensive, and it should be provided for life. Therefore, sponsors do not usually make commitments of this nature before embarking on a trial.

It is probable that Western sponsors have also much to gain from developing countries, but this does not imply that developing countries and their participants are exploited. To be sure, many more steps need to be taken, but many researchers are confident that resources and capacity will be shared within the country, regionally and worldwide.[23]

Conclusion

We have seen that there are indeed many ethical issues to be considered with reference to clinical trials taking place in developing countries. The difficulty of applying Western ideals on poor societies with different cultural and educational status is evident. And, sometimes, motivations of profit can make the sponsors behave in a rather unethical, or even unlawful and violent way. However, it needs to be kept in mind that these negative practices do not take place very often, and that clinical trials are usually conducted on

pp: 243-250
E-ISSN:1791-809X www.hsj.gr

the basis of the widely accepted international principles of ethical research. Developing countries have much to gain from Western sponsors, and international bodies recommend the development of more research programs for these areas. For instance, the European Group on Ethics in Science and New Technologies asserts that 'the funding of research devoted to solving health problems that are specifically acute in developing countries has a value in itself in terms of solidarity. The Group welcomes the EU policy of funding research in developing countries to fight against poverty-linked diseases.

Priority should be given to training local health care professionals in ethical principles, and to organising effective research ethics committees in order to supervise the procedures. Progress may be slow, but, in the long run, clinical trials have the potential to contribute significantly to the improving of health status in developing parts of the world.

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pp: 243-250
E-ISSN:1791-809X www.hsj.gr

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