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Current Debates in Standard of Care in Clinical Trials

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Abstract

Many international regulations that govern human subject's research have been devised keeping in mind, implications of research conducted by researchers of developed countries on human subjects living in developing countries. It is not uncommon for researchers to be drawn to undertaking research overseas. Scientists like sharing experiences, knowledge and benefits of research with colleagues from different backgrounds, and often obtain funding that is directed to specific developing countries. Another legitimate reason is that the disease (their research interest) is prevalent in that particular population. What is worrisome though is that some are driven merely to pursue academic advancement and gain commercial benefits from an enhanced international reputation at the expense of the host community. This leads them to undertake research activities in another country that would not, otherwise, be permitted in their own country, due to ethical or legal constraints. This is where the controversy arises. Is it ethical to allow international collaborative research, the sole intention of which is to benefit from a favorable regulatory scheme in a resource poor country? The answer to this question is not simple, because it poses a grave risk of exploitation of the host community. Exploitation occurs when one party receives an unfair level of benefits or unfair burden of risks as a result of interacting with the other party. Developing countries have limited resources, lack regulatory infrastructure and independent oversight processes. There are financial constraints in addition to cultural and linguistic barriers, illiteracy and limited health care services. A major ethical concern is that certain multinational pharmaceutical giants when faced with a banned drug use third world countries as their dumping ground for redeeming profits. It is unfortunate that in spite of serious health warnings and/or uncertain long term effects; such drugs continue to be widely distributed in developing countries.

Keywords: Standard of care; Research ethics; Clinical trials; Big pharma; Human rights; Drug trials; Harm reduction

Introduction

In early 1980s about 1200 deaths were reported worldwide because of two anti- arthritic drugs phenylbutazone and oxybutazone. Despite being banned or restricted in many developed countries these drugs were being actively marketed by the same companies to the Third World [1]. What was even worse was that the companies used different standards in labeling and marketing their product in developing countries. In recent times, take the example of COX-2 inhibitors celecoxib, or the older drug theophylline still widely used in asthma patients as first line. In Zambia, a 'cure' for AIDS called Tetrasil was promoted by a Zambian newspaper editor who held an ownership stake in the product with a prominent US AIDS denialist [2]. The product was found to be a pesticide used to clean swimming pools. These are just some of the recent Red flags and point toward violation of standard of care.

Defining 'Standard of Care'

So what does 'standard of care' really mean? Unfortunately, standard of care for human participants in research is not well-defined. Roughly, the concept is usually taken to mean 'the best proved treatment for any condition under investigation in a trial' [3]. Another version proposed by the Nuffield Council on Bioethics is as follows: Universal standard of care is the best current method of treatment available anywhere in the world for a particular disease or condition. One the other hand, non-universal standard of care is the treatment available in a defined region [4].

Benatar and Singer propose a more comprehensive definition. It is imperative that when research is being conducted in a developing country, the community's value, culture, traditions and social practices are respected. A team comprising of researchers from the same culture and language group as the subjects should be involved in the project so that the same degree of communication, trust and comprehension is achieved through a legitimate informed decision making process. Not only that, provisions of the same follow-up facilities after completion of the study and the same access to on-going care should be made. These do account for researchers post-research responsibilities and they should be made clear prior to beginning the research. They also argue that the standard of care set by the developed world, in particular, the US, should not be considered the norm and should not be emulated throughout the world. They believe that international regulations like the declaration of Helsinki and other guidelines do not provide the adequate understanding of what is ethical in a certain geographical context and therefore, fall short.

Lessons Learnt From the Tuskegee Trial

The Tuskegee Syphilis Study examined the natural course of Syphilis and it was US government funded clinical trial conducted from 1932-1972.The issue that raged public outcry was that, all 399 recruited participants were African American men in the late stages of syphilis, they were told that they were being treated although the physician researchers had no intention of doing so. When this trial was going on, Penicillin had been discovered and widely accepted and available as

standard of care, for syphilis but penicillin was withheld from these participants .As a result 28 of Tuskegee study participants lost their lives, about 100 suffered from complications of the disease, and the infection was transmitted to their wives and from them to their new-born babies. The participants were kept in the dark about the nature of their illness. There was an element of deception that they were lied to, that they are being treated whereas they were not. Study participants had not given fully informed consent. Neither the purpose of the study was explained to them nor were the risks and benefits made clear. Although gross ethical violations like these happen infrequently today, yet this study raised several important points. Vulnerable populations (minority groups) were especially chosen, because their interests could have been exploited easily. Protection of vulnerable populations became a priority in research guidelines. Also, the study participants had no direct benefit from the study. So later guidelines ensured, that only such research is undertaken that will have social value and the community being researched will stand to gain direct benefit from the research. Important information having huge implications on participants' health was not disclosed to them. It is now mandatory to provide enrolled participants with any new information that arises in the course of the study.

Some Recent Experiences

The renewed interest in the concept of standard of care is because of the clinical trials which tested a new regimen to prevent HIV vertical transmission and enrolled pregnant women in developing countries. They included a placebo arm instead of comparing the new regimen with the best proved treatment available in the developed world. Critics of such trials argued that if the best proved therapy existed anywhere in the world, placebo use was unethical. The World Medical Association says that 'extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy' [5]. Those who carried out the research said that since there was already no provision of basic health care and anti-retroviral medication in that setting, therefore, the use of placebo was justified. They maintained that the host community was not left worst off than it was before the beginning of the trial. However, it is well known that when there is uncertainty about the efficacy of a new treatment, clinical researchers are justified to compare that experimental intervention with a placebo. The critics of this trial argued that a placebo controlled trial becomes unethical when therapies other than the experimental one are judged to be beneficial and are available. In such a case, when the 'best proved therapy' or 'proven effective therapy' exists, any new experimental drug should be tested against this existing treatment (or one that is considered the standard of care). It is important to note that several times this proven effective therapy fails to show superiority to placebo. The root cause of this to be under appreciated is publication bias. It is the tendency for studies that are positive or in favor of a drug to be published and the tendency for negative or indeterminate studies not to. Khan et al reviewed several unpublished as well as published clinical trial data on anti-depressants after acquiring it from FDA through the US freedom of information act [6]. Out of the 92 active treatment arms reviewed, 51% failed to demonstrate assay sensitivity. Assay sensitivity is the ability of the trial to distinguish an effective from an ineffective therapy. In other words, more than half of those new drugs, which were approved by FDA, failed to show superiority to placebo. This highlights the fact that sometimes not using placebo can be unethical. If placebo was not used in these trials, and had compared the drug with the best proved therapy, then there was no way to discover that most of these trials were undertaken for marketing purposes to promote 'me too' drugs. If we were to rely on equivalence studies for new drugs we would risk approving ineffective drugs such as in the above example. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial showed a five-fold difference in the incidence of myocardial infarction in the Vioxx group [6] as compared with the best proved treatment/ the standard of care),naproxen group. This trial did not include a placebo group therefore it remained unclear whether there this fivefold difference was due to an increased risk of myocardial infarction with Vioxx or a decreased risk with naproxen due to its inhibitory effect on platelet function. Almost four years later, and after millions of patients had received Vioxx, it was in a placebo controlled trial that it was revealed that there is indeed increased risk of Myocardial infarction and sudden cardiac death attributed to Vioxx use. Merck had to withdraw the drug and reported several litigations against it filed by the patients.

Conclusion

In view of the above mentioned facts, it is clearly evident that 'research prospectively viewed as undesirable by various interested parties in high-income countries is usually welcomed by those same parties in middle-income countries' [6].

Because the standards of care differ in developing countries, some trials may be allowed there that would be rejected as "unethical" in developed countries. This raises the question of who is better able to define ethical standards for conduct of clinical trials in a given country the research ethics committees of the host country or the high income country. The high income countries who conduct the research are not only unaware of the ground realities and socio political make-up of the host country but in most cases is detached emotionally from and culturally insensitive toward that community. How does one avoid ethical imperialism in this case? [7]. More importantly, should participants in developing countries receive the same standard of care that participants in wealthier countries would receive if the research was conducted there? [8].

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