Debates on "standard of care” in research

Current debates on “ Standard of Care” in Research on Human subjects in the Developing World

- Zoheb Rafique

INTRODUCTION:

For sometimes now, medical and bioethics communities have been facing some of difficult and divisive issues regarding the ethics of the international research. These issues often get fuel, when the interventional research is conducted on the poor and vulnerable people in the poor developing countries. Normal term “ Standard of the Care”, against which some of new interventions and inventions are tested in the medical research has not been adequately defined. This term is often usually taken to mean the “ best proved treatment” for any of the condition under investigation in any of the trial. The debate regarding what constitutes a reasonable and fair standard of care for subjects in the developing countries and those who participate in the clinical trials has been aroused by the critics of the studies on transmission of HIV. Those critics also argued that the placebo controlled trials of the new regimens as to prevent the vertical transmission of the HIV were highly unethical because of the reason that they included the placebo arm rather than “ best proven treatment” which is available in the developed countries. While some of the commentators considered criticisms to be unbiased and associated with imperialistic attitudes. This debate made it very clear that high standards of the research plans to have not been comprehensively and adequately defined. Although there was some justified concern that the pressure from US food and the drug administration could “ dilute” declaration of the Helsinki, and critics were also confident that

whether a trial was ethical could be deduced from text of a declaration. But some declarations such as declaration of the Helsinki, that governing international research ethics are accepted like the constitutions and needing interpretation. Also assuming what is ethical, goes beyond merely following all the prescriptions and also requires some moral reasoning (1). In this article, I will discuss and comment on various debates on standard of care in human research in the developing world.

DISCUSSION

Equal standards of medical care during research, reflecting equal respect for the dignity of subjects, could be taken to mean any one or a combination of several requirements. It is arbitrary and not justifiable to select only one of these, for example, which drugs are used to compare the standard of care in developed and developing countries. In context of some disputed studies on the issue of HIV transmission, the forced emphasis on some “ best proven drugs” having greater considerations of whether those drug regimen can be safely applied in the different settings. Also little attention has been paid to fact there were so many differences between the pregnant women in the developing countries, and in countries where “ best proven” treatment previously been established. The pregnant women in the developing countries present to the antenatal clinics at much later in the pregnancy than women in original studies; they are often malnourished and anemic, and they often live within some context in which the breast feeding having different implications for the newborn infants. Moreover, the advice don’t breast feed would then contradict years of the intensive education by WHO (World Health Organization). Also concerning use of the placebos, the

approach than also been simplistic. A placebo arm is legal and justified in any trial requires some careful consideration of the potential benefits and harms in those specific contexts and they cannot be just simply deduced from any general declaration. And of course it is very necessary to acknowledge the fact that many of the placebo trials are often unethical because they are performed largely for the marketing purposes just to show that “ me too” drugs, have effects and actions greater than those placebo, and rather than to study that they are better than the existing similar, often cheaper, drugs. Also not only should nothing to be done to make it easier to perform such trials, but also each and every effort can be made to reduce and decrease wasting time, money on the “ promotional studies”. In these situations where there are some good reasons for the placebo controlled trials, those should be considered on the merits rather than to be precluded by any bluntly designed clause in the declaration. To protect the host communities from the exploitation, most of the commentators argue that the efforts to improve the health care in developing countries should never ever involve the research that uses and utilizes less than “ Worldwide best” methods, and meaning best of methods available anywhere in this world. Most notably, paragraph 29 of the Declaration of Helsinki states: “ The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods”. The debate over the issue what standard of the care should be required for the individuals participating in the research trials typically focuses on the research conducted in the developing countries by the investigators from the developed countries. This focus makes some sense. Most of the clinical research is conducted by the investigators from the

developed countries, and most of communities lacking the access to good health care are located in developing countries. Researchers from the developing countries can also exploit the host communities. And also the communities in the developed countries lack access to best methods available in the world, and increasing the potential of being exploited. Then a complete analysis, should also address the potential for exploitation and independent of nationality of investigators, and the geographic location of any study (2). When the Helsinki calls for “ the best proven therapeutic method” than does it mean [A] “ the best therapy which is available anywhere in world”? Or does it say [B] “ the standard that is applicable in that country in which drug trial is conducted”? Helsinki is not very clear about this. But I must say that [1] a detailed and careful analysis of document and also its history tells us that the best therapy standard was intended initially and primarily as the standard of medial practice. This conclusion yields another conclusion: that [2] “ the best proven standard of therapy must necessarily be the standard which prevails in that country in which clinical trial is being carried out. In part, interpretations A and B often differ over what I call the question of relevant reference point. Also emphasizing this disagreement makes it appear as the dispute hinges on question of whose medical practice constitutes relevant medical practice. So, the sides of the debate are divided into the proponents of local standard of care and also the critics who often champion the global standard of care. Framing the debate as the question of relevant reference point, however, effectively obscures a more fundamental source of disagreement. To see this, consider a crucial assumption that lies behind following argument. It is sometimes claimed that (1) because content of the standard of care is often

fixed by local reference point and (2) because the prevailing treatment for preventing the maternal-infant HIV transmission in those countries where short-course AZT trials were conducted was no treatment at all, that (3) use of the placebo does not fall below established standard of care. Also it is important to see, however, that in order for (3) to follow from (1) and (2), we have to adopt the local reference point for standard of care(3). The ethics of the placebo-controlled trials to prevent the perinatal transmission of the HIV infection in continents like Asia and Africa have been widely debated. Some critics have argued that it is very unethical to leave the patients untreated when the proven life-saving treatment and therapy is being used in other parts of the world. We note, that conduct of the placebo-controlled trials in any developed country which would be unethical in some other developed country, has evoked some of furor that surrounded HIV perinatal transmission trials. The patients on other hand can choose not to take part in the trials. Reluctance to participate in the trail may be greater when there is some placebo control and the patients are asked to delay and forgo known effective therapy, also large number of the patients regularly agrees to take part in the placebo-controlled trials of the new agents. The perceived scientific value of the trial can contribute to this decision. Although care must be taken to ensure that manipulation of such considerations (e. g., by exaggerating scientific importance of trial), it seems very reasonable to allow the potential study participants to balance these benefits against some potential risk of the participation in this trial (4). Some of the observers noted more than decade ago that the research was conducted in the developing countries without the concern for the adherence of international ethical principles regarding the human subject’s research contained in 1947

Nuremberg code and also in the 1964 Declaration of the Helsinki. This situation has not improved. As for example, two years back, Food and Drug Administration decided that the research studies submitted to it for the review purpose need no longer be bound by Declaration of Helsinki and they must follow only the industry-sponsored Guidelines for the good clinical practice also outlined by International conference on the Harmonization. What is the legal status of Nuremberg code and Declaration of the Helsinki? Are they old outdated ethical rules that the researchers might ignore with the impunity? The question remains open, but just as clinical trials attempting to interrupt mother-to-child transmission of HIV in mid-1990s gave rise to some continuing debate about the global standards of care and also benefit sharing, so another mid-1990s research trial in the continent Africa has brought the international research rules back to the center stage (5). In addition to discussing recent debate and concerning international HIV research, also we should focus on whether or not to randomized, as the controlled trials must be conducted for the researchers to learn about intervention’s efficacy. The choice of the study design is not between ethically questionable perfect trials that produce the complete knowledge versus the imperfect designs that produce no knowledge. Moreover designs, such as the observational studies, that resolve the certain ethical quandaries are not necessarily free of the other ethical problems. One problem is that these studies can provide only limited guidance for the public health policy. The other issue is of informed consent, which is one of corner-stones of the research ethics. The quality of the informed consent is compromised when the potential patient participants believe, wrongly, that the medical care is contingent on their agreeing to participate in the research. Also it is

important to emphasize the potential participants that neither their access to the medical care, nor quality of care they receive, will be affected in any of the respect by their decision. It is sometimes very difficult to clarify this separation of the research from the medical care; the potential participants can be made aware through the effective communication that the decision about the research has no implications for their medical interests. Some more challenging situation occurs when the potential participants rightly believe that the medical care is contingent on their agreeing to enroll in the research (6).

CONCLUSION

The concept of standard of care has prominently figured in the recent controversies over use of placebos in design of the randomized controlled trials conducted in United States and the developing countries as well as the control group selection in critical care RCTs conducted in the United States. The traditional understanding of standard of care to which the physicians are held responsible refers to the typical practice of physicians in professional community. To answer the clinically valuable questions, it is often necessary for the clinical trials to randomize the subjects to interventions that deviate from standard of care in the medical practice. Nevertheless, the control groups that represent standard of care are mostly required to promote clinical value of the randomized trials and also to protect the research subjects. In case of the critical care trials, question whether RCTs should include a control group raises some complex scientific and also ethical issues that call for the careful assessment and judgment (7). In conclusion it is stated that every medical research project involving human subjects should

be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subjects or to others.

REFERENCES:

1. Solomon R Benatar, Peter A Singer. A new look at international research ethics. BMJ. 2000; Vol. 321, 824-826.
2. David Wendler Et Al. The Standard of Care Debate: Can Research in Developing Countries Be Both Ethical and Responsive to Those Countries’ Health Needs? American Journal of Public Health. 2004; Vol. 94, No. 6, 923-928.
3. Alex John London. The Ambiguity and the Exigency: Clarifying ‘ Standard of Care’ Arguments in International Research. Journal of Medicine and Philosophy. 2000; Vol. 25, No. 4, 379-397.
4. Susan S. Ellenberg, and Robert Temple. Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Annals of Internal Medicine. 2000; Vol. 133, No. 6, 464-470.
5. George J. Annas, J. D. Globalized Clinical Trials and Informed Consent. N ENGL J MED. 2009; 360; 20, 2050-2053.
6. Ruth Faden, Nancy Kass. Editorial: HIV Research, Ethics, and the Developing World. American Journal of Public Health. 1998; Vol. 88, No. 4, 548- 550.
7. Franklin G. Miller and Henry J. Silverman. The Ethical Relevance of the Standard of Care in the Design of Clinical Trials. American Journal of Respiratory and Critical Care Medicine. 2004; Vol. 169, 562-564.