Review Article

COMPLEXITIES OF MEDICAL RESEARCH IN DEVELOPING COUNTRIES: STANDARD OF CARE: RESPONSIBILITIES OF ETHICS COMMITTEES**Inayat Ullah Memon**

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Correspondence: Inayat Ullah Memon. Mobile #: 0300-9371766, Email: memon.inayat@gmail.com**Abstract**

Increased awareness of human rights particularly those of vulnerable and emphasis on protection of less strong from stronger groups, have extended the limits of biomedical ethics where human participants are involved in the research. Inequalities amongst various global groups and subgroups in respect to financial resources and health-care with increased collaborative biomedical research, particularly for-profit institutions have raised ethical issues one being the standard of care in research in developing countries. Emergence of newer and complex infectious diseases and resurgence of older ones in recent past has prompted Western world to undertake research in the Eastern hemisphere of the globe. But it has generated complex and various ethical dilemmas. Ethics demands that enrollees of research in developing countries not only be judiciously remunerated but outcomes of the studies be directly beneficial and affordable to them along with provision of parallel benefits. The core point of discussion amongst various partners is the selection from possible choices of standard of care to human participants in less developed countries. While some authors have argued for alternate standards whereas others suggest to compromise on this demand in particular conditions with permission from Ethics Committees. These suggestions, besides empowering the ERCs have put more burden on them to prepare guidelines and resolve the encountered issues where presently available guidelines are inadequate or insufficient. This work provides in-depth discussion and analyses possible alternatives to this complex dilemma.

Keywords: Bioethics, research, standard of care, developing countries, Institutional Review Boards.

Introduction

Increasing awareness of human rights, need for respect of human dignity, protecting interests of weaker groups from stronger ones have delimited boundaries of biomedical ethics beyond the initial domain of assuring individuals', voluntary and independent informed consent in the field of research involving human participants.¹ Financial inequalities amongst different groups of our globe, vast differences in the available health services between neglected and privileged countries, more research being conducted in poor nations in collaboration with financially rich nations and use of human participants in biomedical research in assistance with organizations of rich nations have prompted discussion on consequent ethical dilemmas. The problem of standard of care in research in poor countries is one that attracts ethicists' attention. Moreover, fast emergence / re-emergence of various contagious like AIDS, MDR/XDR tuberculosis, Dengue, Malaria, Leishmaniasis, Zika, Chikungunya, Arboviruses and other infectious diseases like, Crimean Congo haemorrhagic fever, Ebola virus disease and

Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah and Rift Valley fever, in recent past has developed interest of affluent countries to undertake studies in poor countries afflicted by these disorders, simultaneously it has generated multiple ethical dilemmas that are difficult to be completely resolved with existing ethical guidelines.^{1, 2, 3, 4, 5, 6} It is ethical demand that outcome of various studies conducted in poor and neglected countries not only be beneficial but should be free from potential harms. Similar to rich nations, studies in poor countries ensure that research participants are adequately paid, but as opposed to affordable groups there is ethical requirement that additional benefits be made available to those specific groups in particular and relevant poor nations in general, besides the direct beneficial results of the studies being held. ^{1, 2} Current discussions among various researchers, bioethicists, philosophers, sponsoring agencies, pharmaceutical enterprises, various industry professionals and writers about standard of care in research involving human subjects focus mainly on those investigators and sponsors who belong to

developed countries while research is conducted in developing countries. Debate is focused on some issues including:

1. Is it obligatory to provide universally best standard of care to the participants in the developing countries or alternate care (less than the best) is acceptable?
2. If it is necessary for a researcher from developed world to provide universally best available standard of care, does same principle apply to those researchers who belong to developing world and conduct research in their own countries?
3. If the principles are not equally applicable to investigators of developed and developing countries, then what is ethical justification to relax the rules for indigenous researchers or exempt them from provision of universally best standard of care?
4. What are conditions for continuing standard of care and after-research care in developing countries?
5. What is the relationship between standard of care in 'clinical health-care services' and 'research'?
6. If the standard of care in clinical health-care services is altogether absent or sub-optimal in some specific developing countries, then why not the researchers from developed countries (providing less than the universally best available standard of care but at least equivalent to or better than the existing standard of care) be allowed to undertake research? Will it not at least provide better health-care than available in those countries?
7. If researchers are allowed as described in the above paragraph to undertake studies; due to cost-effectiveness will not they be tempted to conduct increasingly more studies in developing countries? If this happens, will it not change the 'developing world' to 'experimental world' or 'world of human-guinea pigs', with resultant exploitation of people of those countries?

2. Why Universally Best Available Standard of Care?

There are many compelling reasons and recommending guidelines to provide universally best available standard of care to participants in the developing world by the international bodies. According to paragraph 29 of Declaration of Helsinki³ the researchers are obliged to meet these requirements, but the same paragraph permits use of less than the best available medical care, as it says:

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo or no treatment, in studies where no proven prophylactic diagnostic or therapeutic method exists.

Later on in the 64th General Assembly of WMA held in 2013, paragraph 33, it has been implied that less than universally best available set of care may be acceptable in certain conditions.³

While the first part of this paragraph necessitates use of

'best current' interventions, at the same time it provides a window for use of placebo and opens avenues for some authority to justify use of placebo or no treatment altogether. If this paragraph of the declaration is respected and followed, who will decide about the existence of proven available treatments? Understandably, best of the minds would consider the Ethics Review Committees the appropriate bodies to decide about it. Commenting on this issue Wendler, Emanuel and Lie⁷ have put forward an alternate way offering some conditions under which less than the best available care can be considered as acceptable. The conditions are: i, scientific necessity, ii, relevance for the host community, iii, sufficient host community benefit and iv, subject and host community's non-maleficence. But these authors have heavily relied upon the Ethics Committee to ensure existence of these conditions and for the safety of the participants. Objections have been raised against above four exemptions allowing less than the universally best standard of care. Hyder⁸ has rightly pointed out that proposed exemptions are mere theoretical and no operational solution has been offered by them. Mamdani⁹ on the other hand, challenges the usual understanding by the term notion 'standard of care' and underscore that just apparent and direct interventions such as medicine supply, health-care workforce and existence of hospitals are neither sufficient nor the sole factors that comprise the notion of 'standard of care', rather facilities and availabilities of quality-food, potable water, sanitary services and transportation infrastructure are also needed to provide quality-standard of care in broader perspective. In this regard, there is no match between developed Western countries and under-developed third-world countries such as of Africa or South Asia in this regard.

In my opinion, decision about the existence of four conditions that could permit the use of less than the best standard of care as suggested by Wendler et al have unfairly burdened the Ethics Committees to adjudicate on these philosophical issues rather than make their decisions based on existing guidelines recommended by international organizations. It is justifiably feared that such burdens will increase the vulnerability of the Ethics Committees of less developed and economically constrained countries, which are already under the influence of strong economic power and robust 'credibility' of the sponsors from developed nations,¹ in addition to the political pressure emanating from their own governments.

3. Why relaxation for Indigenous Researchers?

As pointed out above, if an investigator from developed world is required to provide universally best available care to the participants of the developing country, then why this rule may not be equally applied to researchers of developing countries. If developing nations' researchers are exempted from these requirements and allowed to carry out their research providing prevalent care to the participants then how this difference can be

morally justified. Does affiliation to different groups of nations provide justification for discriminatory standard of care in these situations? Principles of ethical guidelines and actions of ethics bodies demand not only safety of research participants but are bound to deliver justice to the investigators as well. We need strong moral basis providing exemptions to the indigenous researchers. In my opinion, the criteria should not only be based on the geographic regions to which investigators belong, but these should include the geographic region of the participants, their socio-economic status as well. My contention is based on the fact that there is alarmingly wide economic gap between the poor and rich communities within the developing countries, which is beyond the extent observed in the developed world. If the people of less developed countries are expected to benefit from the research carried out by developed world's investigator and it is honestly expected that they will benefit from such research then there is justifiable reason to allow it, if demands of ethical justice are met. My plea is also based on the apprehension that if allowance for relaxation is granted to less developed countries' researchers then investigators of well developed countries will unfairly benefit from this by camouflaging themselves as belonging to developing nations.

4. After-research Care

Another issue in the developing countries regarding standard of care is providing care after the research is over. In Western countries either insurance companies or the strong public health system is in a position to provide it. But in less developed countries the health insurance system is either non-existent or so weak that it is unable to provide after-research care; while the public health system is not robust enough to meet the demands of effective after-research care. According to paragraph 30 of 52nd Assembly of World Medical Association², there is no excuse from providing after-research care to the participants, but it has not specified who would be responsible for this. But Nuffield Council's report 'The Ethics of Research Related to Health Care in Developing Countries',¹⁰ provides quite comprehensive discussion and guiding recommendations in this regard. Here is the ethical dilemma that if neither sponsoring agency nor the researcher from developed country is taking responsibility of providing post-research care, then after successful experiment, such as that of therapeutic intervention for chronic illness, the participants of the poor country due to the heavy costs and need of prolonged supply of that particular medicine, they would be deprived from benefit of that research. Here, again the Ethics Committees have to shoulder the responsibility of making ethical decisions to make balance between protecting the rights of participants and helping to further the potential benefits of scientific research.

5. Standard of Care in Clinical Practice and Research

One wonder, what is the relationship between standard

of care for the research participants and the prevailing health-care for the people of those countries. If a proposed drug to be tested is expected to be little less (say 20%), efficacious than the present available best medicine for that particular disorder but is much cheaper (say 60% or 80%) than the best drug, and by virtue of this the drug is hoped to be affordable for the poor countries, then why this should not be investigated in the community for future use? In support of this view some international guidelines, such as those of CIOMS, recommend that instead of 'universally best' available intervention, 'established effective intervention' be used in those places, where economic factors preclude the research.²

6. Apprehensions when Best Standard of Care is compromised

Some of the third world countries are poor and many people in those countries are passing their lives below the poverty line and have either non-existent or sub-optimal standard of care. If in those locations researchers (including from developed countries) are permitted to undertake studies with standard of care below the universally best available, at least the people will have better than their existing care of health and benefit from the research. There is need to explore ideas like this one. But there is need of caution in this regard as well. There must be effective implementation of measures that participants may not be used as 'experimental human beings' for diseases alien to their regions or communities, and their locations should not be repeatedly visited and revisited by researchers for human experimentations. There are strong reasons that people of those locations due to non-existent health-care system will be lured to the researches and might ignore caring for their health, moreover because of the immediate and apparent benefits offered by the investigators they would be less critical of the ethical issues like informed consent and potential non-maleficence (resulting from delayed harms of the studies). To uphold the moral values and protect the vulnerable communities and groups from economic, health and social exploitation there is need to safeguard weaker communities within the developing countries and also in the poor nations around the world.

7. Increasing Responsibilities of Ethics Committees

To conduct research in developing countries with provision of universally best available care is an ideal situation, perhaps may not be practicable everywhere; but lesser than the best available care raises ethical issues. Simultaneously, prohibiting the research due to non-availability of the best available care is equally important ethical problem. Given the poor economic conditions of the developing countries and relative lack of research expertise, associated with complexities of research in those regions there is need to conduct research without much compromising the ethical requirements. Within developing world different cultural practices such as family autonomy and gate-keeper's

consent; societal and economic variations pose obstacles in the implementation of international ethical guidelines which are already deficient in this respect. The stakeholders are needed to explore the avenues leading to resolution of these problems, as has been suggested by some of the authors,^{4,10, 4, 5, 6} but their solutions might not be the final word and may be objected upon by other partners in the field^{8, 9}. At least the healthy, sincere and honest debate with awareness of the ramifying issues and efforts to resolve them will take us closer to the solution of this important ethical issue confronting the two halves of the globe. This aim is achievable with understanding of the problems faced by the partners in this debate including consideration of the cultural, social, economic, political, linguistic issues inherent and specific to developing nations and legitimate concerns of multi-national corporations.^{1,2,4,12,13,14}

Conclusion

In the prevalent architecture of biomedical research, where international guidelines provide outlines of ethical principles, and ambiguous about the operational aspect of standard of care in developing countries, these are the Ethics Committees who are entrusted to resolve the encountering problems. In the prevailing circumstances of developing nations to help to disentangle the facing dilemma, the Ethics Committees are not only authorized to adjudicate the issue but are also burdened with the responsibility of being fair with both the research enrollees to protect their rights and to research participants to help progress the potentially beneficial research, in the developing countries where violation of human rights are not only frequent but the enforcement of laws governing such rights is weak and difficult to implement.^{15,16} The Ethics Committees, to achieve this aim need to be well trained, intellectually and philosophically seasoned, economically independent and resilient enough to sustain political pressure which is not an uncommon occurrence in the developing countries^{1,2,10} as these are the bodies on which depend the interpretation of presently available ethical guidelines and at many instances international ethical organizations (e.g. Declaration of Helsinki and Nuffield Council and CIOMS) rely on them to make decisions under the recommendations and principles offered by them.

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