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International collaborative trials, placebo controls and The Declaration of Helsinki: need for clarification in Paragraph 32

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Abstract

Inequities in socio-economic and healthcare systems between developed and developing countries have been thrown into sharp relief by globalisation. At the same time, pharmaceutical companies have started conducting clinical trials in developing countries in order to reduce their costs substantially. Together, these two developments create ethical challenges for sponsors and researchers of these trials. One such challenge is that of placebo-controlled trials (PCTs). In this paper we analyse Paragraph 32 of the Declaration of Helsinki referring to PCTs, identifying ambiguities in the wording, and then examine three arguments presented by sponsors of PCTs in developing countries, in defence of such trials. These arguments are: (i) a placebo control provides a definitive answer, and is therefore methodologically superior; (ii) placebo-controlled trials are ethical because they serve the principle of utility, and (iii) interpreting the "best current proven intervention" as the local standard of care allows PCTs to be conducted, if the local standard of care is "no treatment". We argue that PCTs are not methodologically superior; nor are they ethically defensible. Other trial designs conforming to the ethics of research are feasible; the reason for conducting PCTs is expediency. We further propose that, given the global applicability of the Declaration of Helsinki, it is imperative to remove the ambiguities in Paragraph 32. In the context of collaborative trials, when a treatment exists, conducting PCTs is ethically unacceptable, irrespective of the geographic location of the trial. Universal standards ought to be applied universally.

Introduction

Globalisation has brought to the fore inequities in socio-economic and healthcare systems in the developed and developing worlds (1-2). Health spending in the least developed countries is US$11 per person per annum compared to US$1,900-2,000 per person per annum in high income countries. The expenditure in the former is well short of the US$30-40 per person per annum recommended by the World Health Organisation (3), required to cover basic treatment and care for major communicable diseases like HIV/AIDS, TB and malaria (4). Thus, in resource-poor countries, the meagre amount allocated for healthcare results in minimum healthcare provision – sometimes none – for its citizens. This creates a situation in which patients may view enrolling in a trial as the only way to access healthcare (5). From another point of view, the large pool of potential research participants in developing countries is of interest to pharmaceutical companies. These companies reduce their costs substantially by conducting trials in developing countries. These factors together raise the possibility that patients in developing countries may be exploited (6-9), posing ethical challenges for researchers as well as sponsors of clinical trials. Some of the challenges are related to the provision of post-trial benefits to the host community, the use of a placebo in the control arm, and treatment and compensation for research-related injuries.

The Declaration of Helsinki (DoH) is a key document in the ethics of international research involving human participants. It has been revised many times and each time important questions of clarification have arisen. Paragraph 32 of the DoH refers to the use of a placebo control.

In this paper we focus on the use of placebo-controlled trials (PCTs) in developing countries. It begins with an analysis of Paragraph 32 of the DoH, and is followed by the enumeration of three justifications given in favour of PCTs, and our arguments against them.

We use the paradigm case of the short course azidothymidine (AZT) trials in Africa as a backdrop to examine the arguments. In 1994, more than 12,000 HIV positive pregnant women in Sub-Saharan Africa were enrolled in randomised controlled trials of a treatment regimen to prevent mother-to-child transmission of HIV. Randomised controlled trials are considered the gold standard of research in order to establish the safety and efficacy of a drug. This treatment regimen using a short course of the drug AZT was based on the 076 regimen that had been found effective, a little earlier, by the AIDS Clinical Trials Group study 076. The 076 regimen was available to patients in the developed world. However, the short course regimen would be much cheaper than 076. Of the 12,000 women, half were given the test drug (short course AZT) and half were given placebo. This provoked a heated international controversy on the ethics of conducting placebo-controlled trials when an effective treatment – 076 – existed in the sponsoring country (10-11) and eventually led to a number of revisions in the Declaration of Helsinki.

Finally, we conclude that Paragraph 32 of the DoH must state unequivocally that conducting a PCT when treatment exists is ethically tenuous, irrespective of the geographic location of the trial.

The Declaration of Helsinki

The Declaration of Helsinki is the leading international standard of ethical principles for medical research involving human participants (12). Since it was first issued in 1964, it has undergone a number of revisions. The latest revision addresses issues related to post-trial benefits, research-related injuries and the use of a placebo control.

However, the DoH has not resolved the question of whether the use of placebos in collaborative trials is ethical when there is a proven intervention in the sponsoring country for the condition that the experimental drug will treat. (This is of concern because in such circumstances, participants on placebo would be deprived of an effective treatment, thus subjecting them to harm.) As a result, PCTs are still conducted and the debate on the ethics of PCTs is ongoing (13-17).

The DoH was last revised in October 2008. One important clarification was in Paragraph 32 concerning PCTs. The paragraph now reads:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the *best current proven intervention* except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in *studies where no current proven intervention exists;* or
- Where for *compelling and scientifically sound methodological reasons* the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option. (18: para.32)[emphasis added]

Below, we argue that the interpretation of these phrases is not self-evident and, in the context of international collaborative research, these guidelines do not provide clear guidance.

First, it is not clear what the locale is of the "best current proven intervention" against which the new intervention is to be tested. It could be the current proven intervention in the sponsoring country or the current (usual and available) intervention in the host community where the patients are enrolled.

Second, it is not clear whether the phrase "studies where no current proven intervention exists" refers to the geographic location of the study, that is, when a study is conducted in locations where no current proven intervention or treatment exists. It can also be interpreted to refer to the disease under investigation for which no current treatment exists *anywhere*, and the purpose of the trial is to find a treatment. If the phrase means the latter, then the use of a placebo for the control group is acceptable. However, if the phrase refers to the geographic location of the studies, then it feeds into the assumption that a placebo control is permissible in studies conducted in locations where no treatment for that particular disease exists. In the context of international collaborative trials, it leads to the inappropriate conclusion that in countries where no proven intervention currently exists, conducting placebo-controlled trials is permissible, even though the proven intervention exists in the sponsoring country.

Third, the confusion is further aggravated if we permit PCTs for "compelling and scientifically sound methodological reasons". These reasons too can be arbitrary. For example, some sponsors and researchers may have difficulty in designing non-placebo-controlled trials for developing countries.

Following from the discussion above, depending on the interpretation of the phrases, placebo-controlled trials may or may not conform to the DoH's ethical guidelines.

Various arguments are made to support the use of PCTs in developing countries even though an effective intervention exists for the condition to be treated. We discuss these below.

I. Placebo control and definitive answers

One argument in support of a placebo control is that comparing the test drug with a placebo provides a definitive answer to the efficacy of that drug; PCTs will show an absolute benefit. Interpreting paragraph 32 as referring to the geographic location where no treatment exists and supporting it for a "compelling and scientifically sound methodological reason", it is argued that a PCT, unlike an active control trial (in which the control group is given another, effective drug), provides a definitive answer to the efficacy of the test drug (19). This implies that PCTs are able to distinguish between active and inactive treatments and therefore methodologically superior (20). Any study that shows the superiority of a treatment to a control (whether placebo or active therapy) provides strong evidence of the effectiveness of the new treatment (21). Therefore, conducting a PCT would provide a definitive answer and validate the provision of a proven effective test drug in the host country (as in the PCTs of short course treatment to prevent HIV transmission in Africa); governments require convincing evidence about treatment efficacy in order to make sound public health policy decisions regarding allocation of funds (22-23). However, a concern here is that since PCTs can only answer the question of whether something is better than "nothing", even minimal efficacy would appear magnified.

We suggest that alternative trial designs can be formulated in which an effective treatment (available in the sponsoring country) is provided to the control group. Conducting this active control trial would establish whether the investigational intervention is better or worse than, or equivalent to, the standard treatment in efficacy and safety (24-25). And that is what needs to be known: how does the new drug fare when compared with what we are using at present?

A second alternative to PCT is using information sources external to the trial, which can provide a valid and reliable basis for evaluation of the new drug (21). This information can be from historical controls. Yet another methodology could be to start with a small cohort of patients and as soon as the efficacy of the intervention is determined, the data monitoring and safety board could expedite the use of the new drug for the rest of the patients. We suggest this possibility based on the

protocol followed by Sperling et al (26).

Therefore, if paragraph 32 were interpreted to refer only to diseases for which *no treatment* exists *anywhere*, this would represent a justifiable, ethical, use of placebo controls. Once a treatment becomes established, the new drug regimen must be tested against it (27-28).This ought to be implemented wherever collaborative research is conducted, reiterating the ethical interpretation of the phrase; to deny patients effective treatment in order to influence health policy is as bad in developing countries as it is in developed countries (13).

II. Placebo controls and ethics

The second argument in favour of conducting a PCT is based on a principle of ethics, that of utility, which is to always produce the maximal balance of "positive value" over negative value. Resnik argues that PCTs provide quicker and more reliable answers to scientific questions – PCTs are more efficient (29). However, using a utilitarian calculation to justify placebo use in conditions that result in morbidity, and/or mortality, violates the principle of beneficence, even if consent is obtained (30). Resnik further argues that ethical principles sometimes conflict with the scientific rigour of the trial: this argument was based on the assumption that PCTs are methodologically superior and hence beneficence and informed consent may be trumped by "scientific rigour, justice and social utility"(29:298).

However, as shown above, in order that the principle of utility (and beneficence) is not compromised, alternative trial designs can be formulated. Moreover, statistical analysis shows that the number of participants required in an active control trial and a placebo-controlled one is similar (17, 31-32).

It is noteworthy that the phenomenon of placebo effect, wherein the placebo mimics the active drug response (33), can contribute to the variability in outcome data (34). This has implications: if the placebo effect is strong then the number of patients required to overcome this effect will increase (35).

Placebos and justice

The principle of justice may be violated by conducting PCTs. It is plausible that if an active control trial in developing countries identified effective but less expensive and less toxic drugs, then these regimens would be implemented in the developed world (36). Or if the superiority of one drug were to be established over the other when both "ran" against each other, the result could have implications, both therapeutic and economic, in developed countries (37). This can have major financial implications for companies that have already established a market for one drug. If the cheaper regimen turns out to be more effective than the established treatment, or if it turns out to be equally effective, then the companies could lose substantially. In the case of the HIV/AIDS trials, the success rate in reducing mother-to-child transmission was considerably higher in developed countries where the 076 regimen was in use; but not in developing countries, where a short regimen was in use. However, the point to note here is that the knowledge generated through the use of the short regimen in developing countries was used by researchers in developed countries to create more effective treatment regimens for patients in developed countries (38).

Placebos and non-maleficence

PCTs are also beset by another consideration that is both practical and ethical: participants in a trial need to be informed that during randomisation they may be assigned to the placebo arm. However, "potential participants may be more likely to consent to a trial where they are certain to receive an 'active' treatment than they are if they might get a 'placebo'" (31: 43). There may be problems of noncompliance when these patients either do not take the "placebo medicine", or withdraw, or covertly seek treatment (31). As stated earlier, it is the provision of treatment that impels patients to enrol in many trials in developing countries (5, 39-41). Even Miller and Brody who are proponents of PCTs write: "placebo controlled trials raise ethical concerns insofar as they have the potential to exploit the research participants by exposing them to excessive risks from placebo assignment."(42:8).

Placebo and equipoise

An ethical prerequisite for starting a randomised controlled trial is clinical equipoise, a state in which the medical community, on the basis of available data, is equally poised between the two treatments being tested. According to Freedman *et al:*

As a normative matter, it defines ethical trial design as prohibiting any compromise of a patient's right to medical treatment by enrolling in a study…these principles allow for testing new agents…. At the same time they foreclose the use of placebos in the face of established treatment. (32: 244-5)

If the phrase "studies where no current proven intervention exists" is interpreted to mean the location of the trial where no treatment exists, then by conducting PCTs, the indeterminacy of treatment options is lost; that is, *equipoise does not exist because when one compares the test drug with 'no treatment' (placebo) then the advantages of the former over the latter are already established:* placebos cannot treat a disease. Furthermore, randomised controlled trials are phase 3 trials (phase 1 being primarily for safety and phase 2 for safety and efficacy on small numbers of participants) by which time preliminary data from earlier phases provides some information about the potential benefits of the test drug (43) that would suggest that the new therapy is better than placebo (44). We argue that conducting a PCT in the light of such evidence -- where equipoise is lost -- is ethically tenuous. Since science and ethics are not separate, it is necessary that in conducting research on human participants the scientific merit of the research must be matched by the ethical merit of the work (45-46).

III. Placebo control and "standard of care"

This argument in favour of PCTs depends on ambiguities in the DoH. In the past the "current proven method" was interpreted as standard of care (in its narrow interpretation) which was again subjected to varied interpretations. Depending on the

frame of reference, it meant either standard medical practice in the host country or the universal standard of care if the frame of reference was a practice with widespread acceptance among the medical profession worldwide. In other words, it was a normative standard set by the judgement of experts in the medical community, and not a description of the local practice (47).

Similarly, if the phrase "studies where no current proven intervention exists" is interpreted by sponsors as: "studies conducted at locations where no treatment exists"; by deduction, placebo control is acceptable. This argument resonates with the claims that in Sub-Saharan Africa, the local standard of care was "no treatment" and hence use of placebo was justified (37) and left no woman "worse off"; on the contrary at least some benefited from the test drug (23, 48). An argument like this would be unacceptable to ethics committees in a developed country which do not allow PCTs when effective treatment exists, even though these treatments are not accessible to a substantial number of their people (49). If antibiotics are not available in a community, it does not mean that the standard care for infections in this community is "no treatment"; since the standard care for infections is antibiotics. All it means is that the drugs are not available in that community, and this non-availability is determined by vested interests driven by economic considerations (50). No standard can be set in circumstances of deprivation and fiscal constraint, and the argument that "no treatment" is "standard care" at a certain locale is a misinterpretation of Paragraph 32 of DoH, used to substantiate the use of placebos in the control group.

The phrase "studies where no current proven intervention exists" could be misinterpreted to strengthen the arguments for conducting PCTs in developing countries (as did the standard of care debate) but this would contravene the DoH's more unambiguous paragraph: "it is the duty of the physician in medical research to protect the life, health and dignity of the subject"(18: para.11). The guidelines have been formulated so that the subjects' welfare is not subordinated to the objectives of the research and came into being as a consequence of (some) scientists' misadventures. Now, the moral obligation is to avoid acts that would contravene the deontological imperative of the medical profession to "do no harm".

Although Ellenberg and Temple make exceptions to the use of placebo controls in conditions where "temporary discomfort" may occur; omitting proven therapy is not an option where morbidity and mortality may result (51). A trial which places the trial participant's life and health in jeopardy by using less than the effective standard treatment would not be permitted in the sponsoring country; because the "local standard of care is the same as the universal standard of care so anything less would not have sufficient social value to justify its risks"(48:926). Arguably, there are marginalised people in sponsoring countries who do not have access to standard healthcare (52). Even so, the use of a placebo (in the presence of a proven intervention) would not be approved by their ethics review boards. Therefore, if conducting placebo-controlled trials in the sponsoring country is unethical, then exporting them to developing countries is also unethical (53); in other words, the researchers and sponsors are guilty of double standards.

Sponsors of collaborative trials, interpreting the phrase "studies where no current proven intervention exists" as the locale of the study where no treatment exists and buttressing it on "scientifically sound methodological reasons" could then conduct a PCT(6). As established earlier, this claim is not based on scientifically sound reasoning, nor is it ethically valid, hence its removal brings to the surface other reasons for misinterpreting Paragraph 32 and conducting PCTs in the developing world. These are exclusively based on expediency: financial advantage and ease in enrolling patients (7, 9, 30,50,54). In developing countries, research participants' lack of knowledge regarding disease and their rights places them in a position where the interests of science and the "common good" can take precedence over the research participants' own well being (55-56). However "all research subjects are entitled to minimum guarantees that are transnational and non-negotiable" (57:545). Concerns have been raised that some sponsors and researchers, by conducting unethical research, denigrate the integrity of those who perform ethical research (58). In the HIV/AIDS trials conducted in Sub-Saharan Africa, of the 12,000 women participating, 6,000 received the test drug and benefited. The other 6,000 received placebos -- in others words they received nothing. Thus, the researchers knowingly failed to minimise harm to those research participants (53).

When the reason for conducting PCTs in a developing country is financial, it is necessary to remember that healthcare provision in developing countries is minimal and sparse. In such circumstances, it has been argued, high standards should be set by bringing in new resources to deal with old problems (59). The wide disparities in the healthcare systems of the developed and developing countries require a commitment so that people in the latter also benefit from scientific and economic progress and not just peripheral benefits (60). A step forward would be if each successive research project were to leave the host community benefitted; over a period of time a cumulative effect would help reduce this inequity (30).

Conclusion

Pursuing the path of least resistance in order to expedite trials jeopardises the lives (and liberty) of patients living in developing countries; it is morally (and ethically) commendable to design trials (and policies) that help reduce inequities between developed and developing countries and do not promote double standards. The purpose of revising the Declaration of Helsinki is to remove ambiguities and prevent the conduct of unethical trials. Members of the scientific community and ethics review committees ought to be sensitive to the health needs (and rights) of their fellow citizens. They should enter into deliberations so that each successive trial reduces health inequities between the developed and the developing worlds. It is a normative requirement that universal

standards ought to be applied universally.

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Less equal than others? Experiences of AYUSH medical officers in primary health centres in Andhra Pradesh

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Abstract

The National Rural Health Mission (NRHM) includes, inter alia, the establishment of an AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy) component (practitioner, trained assistants, drugs and equipment) in every primary health centre (PHC). However, five years following the launch of the NRHM, the AYUSH mainstreaming scenario is below expectations, riddled with ethical and governance issues. Accounts from AYUSH practitioners at PHCs in various regions of the state of Andhra Pradesh reveal enormous lacunae in implementation: unfilled positions, inequitable emoluments, inadequate or absent infrastructure, assistance and supplies, unethical interpersonal arrangements, and limited support from non-AYUSH personnel. The widespread negative impact of these conditions undermines the value of AYUSH, demotivating both practitioners and patients, and failing to provide the intended support to the public health system..

Introduction

Traditional, complementary and alternative medicine (TCAM) are therapeutic systems distinct from the dominant allopathic system followed in mainstream medical practice. They are classified as "complementary" when employed in tandem with the dominant system, and "alternative" when employed instead of it. The World Health Organisation defines traditional, complementary and alternative medicine (TCAM) as follows (1):

> Traditional medicine: Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.
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> Complementary/alternative medicine (CAM): The terms "complementary medicine" or "alternative medicine" are used inter-changeably with traditional medicine in some countries. They refer to a broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health care system.

Based on its provenance, context and employment, a system may be traditional, complementary or alternative, or a combination of these. For example, ayurveda used concurrently with allopathy in India is "traditional" and "complementary"; homoeopathy used *instead* of allopathy in India is "alternative".

TCAM in the Indian health system

Allopathy is the dominant health care system in India. Non-allopathic therapeutic systems find a place in the formal health system in the country under a department of the ministry of health and family welfare (MoHFW). This department was established as the department of Indian systems of medicine and homoeopathy (ISMandH) in 1995, and renamed the department of ayurveda, yoga and naturopathy, unani, siddha and homoeopathy (AYUSH) in 2003 (2). It governs the education, research, practice and quality of all the systems