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Ethical issues in clinical trials in developing countries

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SUMMARY

The vertical transmission trials conducted in a variety of developing countries by researchers from more developed countries illustrate a variety of crucial ethical issues. Three crucial issues are the injustice of the use of placebo control groups, the coerciveness of the offer to participate, and the exploitation of Third World countries. This paper examines each of these issues separately. It develops a new standard for when such control groups are acceptable. It concludes that the issue of coercive offers is not well founded. It also concludes that concerns about exploitation are better addressed by assurances about the future care of the subjects in the trial than by assurances of availability of the drugs in the country in general. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS: clinical trials; developing countries; placebo control groups; coercion in research; exploitation research

INTRODUCTION

Since the publication of the results of AIDS Clinical Trials Group (ACTG) 076 [1], it has been known that an extensive regimen of zidovudine provided to the mother and to the newborn can drastically reduce (25.5 to 8.3 per cent) the vertical transmission of HIV. Unfortunately, the regimen in question is quite expensive and beyond the means of most developing countries, some of which are the countries most in need of effective techniques for reducing vertical transmission. This realization led to a series of important clinical trials designed to test the effectiveness of less extensive and less expensive regimens of antiretroviral drugs. These trials were conducted by researchers from developed countries in the developing countries which were in need of these less expensive regimens.

These new trials have been very successful. The Thai CDC trial [2] showed a 50 per cent reduction (18.9 to 9.4 per cent) in transmission from a much shorter antepartum regimen of zidovudine combined with a more modest intrapartum regimen. The PETRA trial [3] showed that zidovudine and lamivudine provided in modest intrapartum and postpartum regimens also significantly reduced transmission, whether or not they were provided antepartum. There was

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a trend to more reduction of transmission if they were provided in a short antepartum regimen (16.5 to 7.8 per cent) than if they were not (16.5 to 10.8 per cent). Most crucially, there was no reduction (16.5 to 15.7 per cent) if they were not provided postpartum. Finally, a dose of nevirapine provided both intrapartum and postpartum was shown in HIVNET 012 [4] to significantly reduce transmission (21.3 to 11.9 per cent). In all cases except HIVNET 012, the control group received only a placebo. In HIVNET 012, the control group received a modest regimen of intrapartum and postpartum zidovudine.

As a result of these trials, developing countries with some financial capabilities have the opportunity to drastically reduce vertical transmission by proven less expensive regimens. This constitutes an important contribution of these trials. Unfortunately, the poorest developing countries (including some in which these trials have been run) may not be able to afford even these shorter regimens unless the drugs in question are priced far less expensively for those countries. Efforts have begun to make that possible [5].

There have been many critics of these trials who have argued that they were unethical. Some have gone on to attempt to explain how the information might have been obtained in other more ethical trials while others have not. My focus in this paper is not on that question. Instead, I want to focus on the arguments offered in support of the claim that these trials were unethical. I see the critics as advancing three very different criticisms, although the critics often do not carefully distinguish them. We will do so to enable each criticism to be analysed. The first criticism is that an injustice was done to the control group in each of these trials (with perhaps the exception of HIVNET 012) since they were denied proven effective therapy as they only received a placebo. The second criticism is that the participants in the trial were coerced into participating, and did not give voluntary consent, because they had no real choice about participating since antiretroviral therapy was otherwise unavailable to them. The third criticism is that the countries in question were exploited by the investigators from the developed countries since they were testing the effectiveness of regimens that would not be available after the trial to the citizens of the countries in which the trials were conducted.

THE JUSTICE OF THE USE OF THE PLACEBO CONTROL GROUP

The scientific importance of the use of concurrent placebo control groups is well illustrated by the PETRA trial. If there had been no such control group, and the various regimens had been compared to the historical control group in ACTG 076, then the intrapartum-only arm would have been judged a success, since its transmission rate was only 15.7 per cent as compared to the 25.5 per cent transmission rate in the control group in ACTG 076. However, it actually was no better than the placebo control group in PETRA (16.5 per cent). When the rate of transmission varies from one setting to another, you really cannot use historical control groups. Despite this scientific value, the critics have argued that it was wrong to use a placebo control arm because the patients in that arm were being denied a proven therapy (the 076 regimen) and were being offered nothing in its place [6]. The critics claim that this did not meet the standard found in earlier versions of the Declaration of Helsinki (World Medical Association, Declaration of Helsinki, Principle II.3) ‘In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method.’

Defenders of these trials quite properly note that none of the participants in these trials would otherwise have received any antiretroviral therapy, so nothing was being denied to them that they would otherwise have received. How then, ask the defenders, can the members of the control group have been treated unjustly? This led to a proposed, very controversial and eventually rejected, revision of the Declaration of Helsinki which read: 'In any biomedical research protocol every patient-subject, including those of a control group, if any, should be assured that he or she will not be denied access to the best proven diagnostic, prophylactic, or therapeutic method that would otherwise be available to him or her.' [7]. The point is then that the justice or injustice of what is done to the control group depends on what the members of that group *would* have received if the trial had not been conducted.

While the reality of what the members of the control group would have received is obviously relevant, I am not satisfied that this proposed revision would have properly taken that into account. Would it be just, for example, to use such a placebo control group in a trial in a developed country where the antiretroviral therapy is widely available except to members of some persecuted minority from whom the control group is drawn? They *would* not have received the treatment if the trial had not been conducted, although they *should* have given the resources available in the developed country. Their use in a placebo control group is not therefore justified. The proposed revision made too much reference to what would have occurred and not enough to what should have occurred.

A recent workshop proposed instead that 'study participants should be assured the highest standard of care practically attainable in the country in which the trial is being carried out' [8]. This seems better, although it may suggest too much. Suppose that the treatment is practically attainable but only by inappropriately cutting corners on other forms of health care which may have a higher priority. I would suggest therefore that the normative nature of the standard be made explicit. It would then read that all participants in the study, including those in the control group, should not be denied any treatment *that should otherwise be available to him or her in light of the practical realities of health care resources available in the country in question.* The question for IRBs reviewing proposals for such research is then precisely the question of justice.

On that standard, the trials in question were probably not unjust, although there is some debate about the THAI CDC trial in light of donated resources that became available in Thailand between its being planned and its being implemented [9]. Such trials will be harder to justify in the future given the current availability of proven much less expensive therapies which should be available even in some of the poorest countries. It is of interest to note that HIVNET 012 was not a placebo controlled trial, but it was a superiority trial, and active controlled trials are less problematic scientifically when they are superiority trials. That may well be the way future transmission trials will be run.

COERCIVE OFFERS

It has been suggested by other critics that the participants in these trials were coerced into participating because of their desperation. 'The very desperation of women with no alternatives to protect their children from HIV infection can be extremely coercive', argue one set of critics [10]. One of the requirements of an ethical trial is that the participants voluntarily agree to participate, and how can their agreement to participate be voluntary if it was coerced?

This line of thinking is analogous to the qualms that many have about paying research subjects substantial sums of money for their participation in research. Such inducements are often rejected on the grounds that they are coercive, because they are too good to refuse. The ICH Guidelines for Good Clinical Practice is one of many standards which incorporate this approach when it stipulates that the 'IRB/IEC should review both the amount and method of payment to subjects to assure that neither present problems of coercion or undue influences on the research subject' [11].

Normally, coercion involves a threat to put someone below their baseline unless they co-operate with the demands of the person issuing the threat [12]. As the researchers were not going to do anything to those who chose not to participate, they were clearly not threatening them. Further evidence of this comes from the reflection that threats are unwelcome to the parties being threatened, and there is no reason to suppose that the potential subjects saw the request to participate as something unwelcome. Even the critics recognize this. The potential subjects were being offered an opportunity that might improve their situation. This was an offer 'too good to refuse', not a threat.

Should we expand the concept of coercion to include these very favourable offers? There are several reasons for thinking that we should not. First, it is widely believed that offering people valuable new opportunities is desirable. Moreover, the individuals in question want to receive these offers, and denying them the opportunity to receive them seems paternalistic or moralistic [13]. It is important that participants understand that what they are being offered is a chance to receive a treatment that may reduce transmission (since this is a randomized placebo controlled trial of a new regimen), and ensuring that is essential for the consent to be informed. As long as care is taken to ensure that this information is conveyed in a culturally sensitive fashion, and is understood, then there seems to be little reason to be concerned about coercion simply because a good opportunity is being offered to those with few opportunities.

A colleague and I are currently working on one residual concern in this area. It has to do with studies in which there is a potential for long term harms to subjects which they inappropriately discount because the very substantial short term benefits cloud their judgement. This may be a ground for concern in some cases, but it is difficult to see how it would apply to the vertical transmission trials. For those trials, it is appropriate to conclude that concerns about coercion were unfounded.

EXPLOITATION OF SUBJECTS

The final criticism of the trials is that they are exploitative of developing countries and their citizens because the interventions in question, even if proven successful, will not be available in these countries. To quote one of the critics: 'To use a population as research subjects because of its poverty and its inability to obtain care, and then to not use that knowledge for the direct benefit of that population, is the very definition of exploitation. This exploitation is made worse by the fact that richer nations will unquestionably benefit from this research...[they] will begin to use these lower doses, thereby receiving economic benefit' [14].

There are really two claims being advanced in that quotation. The second, that the developed countries ran these trials to discover cheaper ways of treating their own citizens, is very implausible since pregnant women in developed countries are receiving even more expensive

cocktails of drugs both to treat the woman and to reduce transmission. The crucial issue is whether the trials are exploitative of the developing countries.

There seems to be a growing consensus that they are exploitative unless certain conditions about future availability in the country in question are met. The Council for International Organizations of Medical Sciences (CIOMS) is the source of this movement, as it declared in its 1992 guidelines that 'as a general rule, the initiating agency should insure that, at the completion of successful testing, any products developed will be made reasonably available to residents of the host community or country' [15]. A slightly weaker version of this requirement was adopted by a recent workshop which concluded that 'studies are only appropriate if there is a reasonable likelihood that the populations in which they are carried out stand to benefit from successful results' [16].

This growing consensus is part of what lies behind the effort to secure these benefits by negotiating more favourable prices for the use of the tested drugs in developing countries. It seems highly desirable that this goal be achieved, but I want to suggest that it should be viewed as an aspiration, rather than a requirement, and that a different more modest requirement must be met to avoid charges of exploitation.

A good analysis of exploitation is that it is a wrong done to individuals who do not receive a fair share of the benefits produced by an activity in which they take part, even if they receive some benefit [17]. This is why a mutually beneficial activity, one from which both parties will be better off, can still be exploitative if one of the parties uses their greater bargaining power to harvest most of the benefits and the other party agrees because they need whatever modest benefit is being left for them.

As we apply this concept to the trials in question, we need to ask who needs to be protected from being exploited by the trials in question. It would seem that it is the participants. Are they getting a fair share of the benefits from the trial if it proves successful? This is a particularly troubling question when we consider those in the control group, whose major benefit from participation may have been an unrealized possibility of getting treated. If we judge that the participants have not received enough, then it is they who must receive more. An obvious suggestion is that *they* be guaranteed access to any regimen proved efficacious in any future pregnancies (or perhaps even that they be granted access to antiretroviral therapy for their own benefit). This would be analogous to familiar concepts of subjects receiving continued access to treatment after their participation in a trial is completed.

I certainly support every reasonable effort to increase access to treatments which will reduce vertical transmission, but imposing the types of community-wide requirements that have been suggested, but not necessarily justified if the above analysis is correct, may prevent important trials from being run because of the potential expense. Such proposals should be treated as moral aspirations, and exploitation should be avoided by focusing on what is owed to the subjects who have participated in the trials. It is they, after all, who are primarily at risk for being exploited.

CONCLUSIONS

These observations are about research in developing countries in general, and not just about research on vertical transmission. Three lessons have emerged. The standard for when a placebo control group is justified is a normative standard (what they should have received if

they were not in the trial) rather than a descriptive standard (what they would have received if they were not in the trial). Coercion is not a serious concern in trials simply because attractive offers are made to the subjects. Legitimate concerns about exploiting subjects should be addressed by ensuring their future treatment, rather than by asking what will happen in their community at large.

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