The Ethics of Placebo-Controlled Trials in Developing Countries to Prevent Mother-to-Child Transmission of HIV

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Abstract

Placebo-trials on HIV-infected pregnant women in developing countries like Thailand and Uganda have provoked recent controversy. Such experiments aim to find a treatment that will cut the rate of vertical transmission more efficiently than existing treatments like zidovudine. This scenario is first stated as generally as possible, before three ethical principles found in the Belmont Report, itself a sharpening of the Helsinki Declaration, are stated. These three principles are the Principle of Utility, the Principle of Autonomy and the Principle of Justice. These are taken as voices of moral imperative. But although each has intuitive appeal, it can be shown that there are possible scenarios in which they give conflicting prescriptions. To achieve consistency, one must be subordinate to the others. The voice of utility is taken as subordinate to those of justice and autonomy and it is shown that given plausible assumptions about the level of poverty and education in the developing country targeted, the experiment is ruled morally wrong in the name of both justice and autonomy. Moreover, it is argued that no justification can be found for the inclusion of a placebo group, when strictly defined. By contrast, a 'no-treatment' control arm might be justified, but only when the demands of autonomy are satisfied, demands that are more stringent than they might appear. A utilitarian defence of the experiment is examined, namely that the would-be participants are in a no-loss situation, and it is shown that this defence is seriously flawed. Finally, it is concluded that there is no justification for amending the Declaration of Helsinki.

***Ann Acad Med Singapore* 2000; 29:557-62**

Key words: Autonomy, Consistency, Justice, Utility

Introduction

Placebo-trials on HIV-infected pregnant women in developing countries like Thailand and Uganda[1,2] have provoked recent controversy.[3,4] Such experiments aim to find a treatment that will cut the rate of vertical transmission more efficiently than existing 'gold standard' treatments like zidovudine. Is such an experiment morally justified? I think that the right question to ask is this: "Is it always, never or sometimes, morally justified to experiment on HIV-infected, pregnant women in developing countries (by means of placebo trials) in order to develop a new treatment X which will reduce the rate of mother-to-child HIV transmission more effectively than the existing ('gold standard') treatment Y?"

Three Ethical Principles and How They Conflict

Put like this, the issue acquires a level of generality. For example, the specific country in which the experiment is carried out is not the issue. Unless there are clear differences from country to country which are morally relevant to the question above, our answer to it should be the same whatever the country in which such experiments are conducted.

Extracting a clear and consistent answer is not easy, given the emotional horror that surrounds even a suitably generalised question. The consequences of the disease are horrible and threaten to multiply through successive generations. The horror is accentuated by the innocence of the foetus as a recipient of those consequences, an innocence that remains regardless of the academic question of whether the foetus is a person or merely a potential person. Add to this the perplexing conundrum of placebo, with its levels of ignorance. Finally, we must contextualise the problem against the background of the horrors built into developing countries, such as unequal and inadequate resources, lack of education and poverty.

Where is a doctor or a researcher to look for guidance in such a case? 'Conscience', isn't any substantive answer, since differing consciences of doctors are just differing internalisations of some medical code. However, there is

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an authoritative code of medical practice, which provides guidance, namely the Belmont Report.[5]

The Belmont Report provides an excellent sharpening of the principles laid down in the unmodified Helsinki Declaration.[6] In essence, it urges three principles: the Principle of Utility (there called Beneficence), the Principle of Autonomy (there called Respect for Persons) and the Principle of Justice.

The Principle of Utility has a negative and a positive form. Its negative form states that

PB neg) It is one's duty to refrain from doing harm

while its positive states that

PB pos) It is one's duty to minimise harm and maximise benefit, *to society in general, including that of future patients*.

The Principle of Autonomy claims that individuals should be treated as autonomous agents, and that persons with diminished autonomy are entitled to protection. In other words,

PA) It is one's duty to respect autonomous choices and to protect those with diminished autonomy.

The Principle of Justice states that 'research should not unduly involve persons *from groups unlikely to be among the beneficiaries* of subsequent applications of the research'. The spirit of this principle is that

PJ) It is one's duty to distribute benefits (of research) fairly

or at least, not worsen the imbalance of benefits and burdens of research among relevant groups.

These three voices of utility, autonomy and justice cannot, in themselves, provide clear guidance in all cases, since there are possible scenarios in which they give conflicting rulings. It seems reasonable to think that the negative voice of utility is not a total prohibition of any form of harm, such as a slightly painful injection. Rather it should be read as 'Do not cause more harm than benefit to a single individual', but this may still conflict with the positive voice of utility. Suppose that the general increase of good over harm to society in general (by means of a reduction of the number of children who will be born with HIV) can be purchased only at the cost of exposing the mothers in the experimental group to a risk of substantial harm that is greater than the chance of slight benefit. Since such exposure is itself a type of harm, the voice of utility is confused.

Now consider the cost to the mothers in the control group. Their babies are effectively condemned to HIV infection, the incidence of which could have been reduced by giving them the 'gold standard' standard treatment Y (for example, zidovudine) that is known to be effective in cutting the rate of vertical HIV transmission. In the name of both babies and their mothers, the negative voice of utility prohibits the experiment, while its positive voice demands it. Suppose further that HIV-infected mothers can only be recruited for the experiment by coercing them to participate or by withholding information about the risks involved (the absence of any effective treatment in the case of the control group and the risks-compared-to-benefits of treatment X in the case of the experimental group) relative to the benefits available to others (by means of the existing treatment Y). Here the voice of utility contradicts that of autonomy, since informed and free choice to participate has been ruled out. Or suppose that the treatment X, once available, will be restricted to a minority of HIV-infected pregnant women in countries wealthy enough to afford it, excluding those in the developing country in which they were originally developed. Even if we could be sure that the rate of vertical transmission would decrease world-wide, in line with the voice of utility, we would still hear the cry of injustice.

One Hierarchy of the Three Ethical Principles

These examples show that the principle of utility will contradict those of autonomy and justice in cases that are at least possible. This means that we must decide in advance which voice has authority over which. As a matter of fact, most of us hear the least authority in the voice of utility. In examples such as those just considered, most will judge that maximising utility at the cost of injustice or at the cost of disrespecting the free choices of people (thus treating them as means to the end of increased health world-wide) is morally repugnant. Thus, one way to achieve consistency among the three principles that will fit the moral intuitions of many is to hold that *the voice of utility must be obeyed, but only after the voices of justice and autonomy have been obeyed*. Those who hear things that way will not be swayed in the least by the tinkering with the original wording of the Helsinki Declaration which was sent to the World Medical Association's member associations in advance of the World Medical Association Council Session in Santiago, Chile on April 15, 1999.

Working from the background of the question towards empirical specifics, the Principle of Justice is the most effective choice of principles to apply first. If the degree of poverty of most pregnant HIV-infected mothers in the developing country (such as Uganda) will prevent them from buying the improved cure, if found, for several generations of HIV-infected offspring to come, while most of the relatives of the researchers (such as Americans) will be able to buy it as soon as it hits the market, then surely this is injustice. As for other scenarios, surely enlarging the relative size of burdened group versus benefiting group

proportionally worsens the injustice. Given that injustice will be done, there is something morally wrong with the experiment, quite regardless of whatever else is ruled wrong by the other principles. Taking the three principles as a guide to procedure, we must at least postpone such experiments until enough economic aid has been given to these countries as makes the chances of benefit more fairly distributed. Otherwise the researchers should experiment upon their own extended geo-political-economic kin. Given the commercial hegemony of the rich drug companies involved, their opposition to the production of cheaper 'generic' drugs and the huge disparity between levels of wealth in developing countries and developed countries, the chances of benefit to the burdened group were clearly *not* fairly available to them.

Let us now suppose (hypothetically but implausibly) that equality has been redressed or is not the issue. What does the voice of autonomy tell us? There are two groups for whom it could speak, the foetuses and their mothers. Clearly the foetus is incapable of making choices, informed or not, so whether or not we say that they are potential persons or already persons, there can be no autonomous choices made by them which are respected or disrespected. In this respect, the voice of autonomy is neutral on the permissibility of the experiment. On the other hand, the principle of autonomy also commands us to 'protect those with diminished autonomy', which appears to include the foetus. If so, on balance, the voice of autonomy prohibits the experiment in the name of the foetus.

It might be objected that the class of those entitled to protection excludes non-persons such as the foetus. This objection clearly has little bite against those who hold that the foetus is to some degree a person at some stage in its development. Nor is it persuasive against those, including the mothers, who think that whether the foetus is an actual or potential person, it is still something valuable, which therefore needs protection.

How does autonomy speak for the mothers? It clearly prohibits the experiment unless the mother has made an autonomous choice to participate. Autonomous choices must be informed choices. In the case of a non-placebo experiment in which the new treatment X is to be tested, this means that the mother must understand the risks and probable benefits to herself and her foetus posed by the new treatment X, *as compared to risks and probable benefits conferred by the existing treatment Y*. Since the probability of risks and benefits of the new treatment may be precisely what the experiment is designed to discover, it may not be possible to give her precisely this information. In that case, the mother must be informed of *the degree of uncertainty* of the probability of possible harms and benefits of the new treatment X, *as compared to the degree of certainty already established* of the probabilities of harms and benefits of the existing treatment Y. Anything less would not be full information.

Complications Arising from Placebo Control

In the case of a placebo experiment, things are more complicated. Placebos aim to separate the causal powers of X from the causal powers of the belief in those causal powers. For example, they aim to filter out cases in which a patient feels better simply because that patient believes (correctly or incorrectly) that the treatment will work. The belief in question may be held by the mothers or the experimenters or both. Clearly no such belief can be held by the foetus. Assume a simple single-blind placebo control in which each mother has a fifty-fifty chance of being selected for the control group to receive sugar as opposed to the experimental group to receive the new treatment X, such that no mother will know which group she is in. Obviously, this design of experiment rules out informing the mothers which group they are in, but this does not mean they can be given no information at all. Autonomy demands that each mother understand that she has a half-chance of ending up in the control group, in which case her foetus will certainly be born with HIV and a half-chance of ending up in the experimental group, with possible risks and benefits to the foetus which are uncertain. *She must also understand that she faces these two outcomes in the teeth of the knowledge that treatment Y already exists, with its more certain risks and benefits to the foetus*.

It might be objected here that the lack of education among such mothers renders them incapable of understanding such information. If so, autonomy demands that education be a more pressing priority than medical research. The experiment must be postponed until the would-be participants are educated to a level that enables them to understand what choices are open to them. Since justice demands that the benefits of education be fairly distributed throughout the developing country in which the experiment is to take place, this means that the experiment must be postponed until any would-be sub-group of participants has a level of education that is representative of the whole population of that country.

This brings us back to the purpose of the placebo. Suppose that an HIV-infected pregnant woman believes that she is receiving a new miracle drug that carries an ironclad guarantee of protecting her foetus from infection. In fact her belief is mistaken, for the drug she has been given is just sugar. It seems unlikely that her belief could have any positive psychological effect upon her foetus. In terms of the mother, the placebo seems to serve no useful purpose. So far, there is no justification for the creation of the control group, in which the foetuses are condemned to

HIV infection. Thus the only other purpose that the placebo can serve is to separate the causal powers of X in reducing vertical transmission from the causal powers of the beliefs of the experimenters. A double-blind trial, in which the experimenters do not know which mother is receiving sugar or receiving X, will ensure that they will not bias the development of one group of foetuses over the other, by giving different levels of care to the two groups of mothers. The question to ask now is whether the increased accuracy of the results of the efficiency of X is worth the price of allowing the mothers in the control group to go untreated. The voice of autonomy tells us that the price need not be paid. Since mothers in both groups are persons equally deserving of care and respect, the experimenters have a duty to provide both groups with the best possible level of care, *regardless* of their beliefs about whose foetuses are most likely to be protected from vertical transmission. Once this duty is discharged, there is no possible justification left for the inclusion of the placebo group.

Thus there appears to be no need for a placebo group at all. Surely the ethical procedure would be to *give the control group treatment Y instead.* After all, are we not trying to measure the difference in effectiveness of the new treatment X *as compared to* the existing treatment Y? If the participants in both groups were fully informed of the experimental set-up, there would be no room for objection on grounds of autonomy, nor any room for objection on grounds of utility to the treatment of the participants in the control group, since this group is assured of the best known treatment available anyway.

Given my definition of a placebo as a control which aims to separate the causal powers of a treatment from the causal powers of belief (or faith) in that treatment, there is, strictly speaking, a conceptual difference between a placebo group and a 'no treatment' control group, which aims to help isolate possible unwanted side-effects of the treatment. In experiments to develop new treatments that are more effective in reducing the vertical transmission of HIV, a 'no treatment group' would help to isolate unwanted side-effects of the new treatment on the foetus. I now turn to this issue.

'No-Treatment Groups' within Controlled Studies

Similar moral objections can be made to different kinds of experiments such as the Rakai project in Uganda,[7] in which the experimenters studied the effect of other sexually transmitted diseases on the rate of heterosexual transmission of HIV and the natural risk factors that determine the heterosexual transmission of HIV-1 over periods of unprotected sex. Such experiments use a 'no-treatment' group within a controlled study. Such an experiment is ruled unethical on the grounds of autonomy, if those who were left untreated were not fully informed that this was precisely what would happen to them. By the experimenters' own admission, those in the 'no-treatment' group were not fully informed. Quinn et al[8] reported that 228 HIV-infected couples were left untreated for up to thirty months, and the decision to inform the uninfected persons that their partner was infected was left up to the infected persons themselves, although the experimenters regularly saw both. Surely this does not count as discharging a duty to give all parties concerned the full information. To so discharge it, the experimenters should have told each couple that one partner was infected *as well* as telling them that the infection would go untreated.

In the same project, the investigators treated half of the villagers for sexually transmitted diseases such as syphilis while leaving the other half untreated. Their aim was to determine the effect of concurrent sexually transmitted diseases on the heterosexual transmission rate of HIV. Assume for the sake of argument, that this information was obtained and that it helped to develop more effective ways of cutting the HIV transmission rate. In terms of maximising the utility to society in general, the investigators were morally justified. Moreover, anyone who maintains consistently that *the voice of utility always overrides the voices of autonomy and justice* can defend the investigators, but that is not the moral framework I have suggested. Given that utility is subordinate to autonomy and justice, we need to ask whether the investigators infringed the informed choices of the villagers who were left untreated. Deciding this is not easy. One way to look at it is to say that the untreated villagers were simply left alone by the investigators to carry on as before, so no interference took place. On the other hand, there is a clear sense in which the untreated villagers were *selected* by the investigators to form one half of the experiment. In this sense, they were intentionally included in the experiment by default. Therefore the voice of autonomy demands that the experimenters give them an informed choice to continue to participate, which in turn means telling them that they would go untreated. Had the villagers heroically agreed to forgo treatment for the sake of future generations then there could be no objection in the name of autonomy. Otherwise, continuing to include them in the experiment would be morally wrong. Against this, it might be objected that the investigators were not doing anything extraordinary, since the villagers would not have been treated in the ordinary course of events anyway. However, it is not so clear that this means the investigators were not interfering. Given that the investigators selected this particular group of villagers for the control arm of the experiment, and then continued to withhold both treatment and information when they could easily have supplied both, were they not interfering? In *selecting* and then ignoring them, surely the investigators were actually *doing* something to them.

The scenario of the untreated villagers is no different in principle from that in which a group of pregnant HIV-infected mothers is left untreated as a control to a second group who are given a new treatment X, in order to help obtain information on (among other things) whether X will have unwanted side-effects on the foetus. Assume, for the sake of argument, that the information is obtained and that it is instrumental in reducing harmful side-effects to babies who are in general, less likely to be born with HIV (than when their mothers were treated with the original drug Y). Again, the voice of utility permits, even demands, the inclusion of the 'no-treatment group', but again, given that utility is subordinate to autonomy and justice, we need to ask whether the investigators infringed the informed choices of the mothers who were left untreated. If the investigators first selected them as a control arm and then withheld treatment and information (including the information that they were infected and that treatment was available), then the mothers' autonomy was violated.

The Utilitarian 'No Loss' Defence

Some commentators[9] in the debate have argued that most HIV-infected pregnant women in developing countries would not be able to afford any sort of treatment against vertical transmission anyway. Thus the women in the original experiment are in a no-loss situation. They have a half-chance of ending up in the placebo group, in which case they are no worse off than they would be anyway and a half-chance of ending up in the experimental group, in which case they have a secondary chance (the degree of which is yet unknown) of protecting their foetus.

This argument suffers from a number of flaws. Are the women in the placebo group really no worse off than they would have been had they never participated? If autonomy has been satisfied, then the women will know that they are in a kind of desperate lottery that holds out a chance for the well-being of their unborn. Since the chances of protection for the foetuses in the experimental group are less than certain, they should know that overall, the odds are against them. Nonetheless, some basis for hope exists, which may well be the very reason why they have agreed to participate. Yet the experimenters know in advance that for each mother in the placebo group, all hope will be dashed. This burden of false hope and its certain disappointment surely represents a significant cost to this group of mothers.

The no-loss argument gains its plausibility from the claim that the personal utility of the volunteers is not decreased. But it ignores the salient fact that the volunteers start from a position of inequality. Were justice done, the proven, if limited benefits of the existing treatment Y would be distributed fairly throughout the world to those in developing countries who need them most. Given that the inclusion of the placebo group is justified, the autonomous choice of the mothers would then be the more heroic one of taking a half-chance of no protection for their unborn and a half-chance of the uncertain degree of protection conferred by treatment X, *in preference to* the guarantee of the certain but limited degree of protection conferred by the existing treatment Y. Given, as I suggested above, that the inclusion of the placebo group is *not* justified, the autonomous choice of the mothers would then be the less heroic but still courageous one of *trading* the certain but limited degree of protection conferred by treatment Y for the possibly improved but uncertain degree of protection conferred by treatment X.

In the original experiment, even those mothers who end up in the experimental group are doubly wronged. Firstly, they are wronged both in the name of justice and in the name of autonomy by being unfairly denied the choice of treatment Y. Then the experimenters restrict their choices to the options of no treatment (by refusing to participate) or the option of a half-chance of the uncertain benefits of treatment X (by consenting to participate). The restriction is genuine, since it is always within the power of experimenters to offer treatment Y as well. Since this is a perpetuation of the original injustice and an erosion of autonomy, this is a further wrong. In this respect, the would-be participant resembles a workman who has been unfairly denied any payment. His employer offers to toss a coin. If the coin comes down heads, the workman will receive half his wages; if tails, nothing. If he refuses the bet, again he gets nothing. The workman is first wronged by being deprived any payment. When the bet is offered, he has nothing further to lose. Yet surely the offer of the bet is a second wrong since it perpetuates the original deprivation of full payment, one that the employer is in a position to put right.

Effects of Modifying the Declaration of Helsinki

Whereas the current Declaration assures research participants of 'the best proven diagnostic and therapeutic method,' the corresponding section in the modified Declaration adds the phrase 'that would otherwise be available to him or her.' This appears to vindicate the 'no loss' argument, since there is no treatment available to the would-be participants in the experiment should they not participate, given that they are too poor to afford any treatment, including treatment Y. But this vindication is an illusion. For one thing, there is an ambiguity in the phrase 'available'. On one reading, treatment Y is not available to the group in the sense that they would not have been able to obtain it, *had they never come in contact with the experimenters*. However, in that sense, since the best treatment available otherwise is none, this amendment is just another way of saying that the group in question is

assured of no treatment. We should therefore reject this amendment to the Declaration, in the name of both justice and utility as originally voiced by it. Utility demands that the benefit to society be maximised and justice demands that this benefit be fairly distributed. In other words, the group in question must be given a fair chance of treatment Y. The other, more sensible, reading of 'available' is that treatment Y is not available to the group *as would-be participants who are now in contact with the experimenters*. However, in this sense, treatment Y *is* available to them even if they now choose not to participate, since it is fully within the experimenters' power to provide it. Thus even the modified declaration tells us that the experiment is morally wrong.

Conclusion

Given plausible assumptions about the level of poverty and education in the developing country targeted, the placebo-controlled trials of the type discussed are unethical violations of both justice and autonomy. In any case, no moral justification can be found for the inclusion of a placebo group. By contrast, the inclusion of a 'no control' group may be justified, but only when the experimenters have not interfered with the autonomy of its members. Experiments such as the Rakai project in Uganda are such unethical violations of autonomy. The development of third-world countries, in the form of economic development and education, must be priorities that come before such experiments.

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