Clinical research in developing countries: recent moral arguments

Pesquisa clínica nos países em desenvolvimento: argumentos morais recentes

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Abstract *During the 1990s, bioethicists raised questions about certain clinical trials conducted in developing countries. These inquiries led to revisions in the Declaration of Helsinki and recommendations from the US National Bioethics Advisory Commission. This article raises doubts about the original questions and subsequent recommendations. It is possible that impractical solutions have been proposed for nonexistent ethical problems.*
Key words *Research Ethics; Clinical Research; Informed Consent; Developing Countries; Declaration of Helsinki*

Resumo *Durante os anos 90, bioeticistas levantaram questões sobre determinados ensaios clínicos realizados em países em desenvolvimento. Tais questionamentos levaram a uma série de revisões na Declaração de Helsinki e a recomendações pela Comissão Consultora Nacional em Bioética, dos Estados Unidos. O artigo levanta dúvidas sobre as questões originais e as recomendações subseqüentes. É possível que soluções impraticáveis tenham sido propostas para problemas éticos inexistentes.*
Palavras-chave *Ética na Pesquisa; Pesquisa Clínica; Consentimento Informado; Países em Desenvolvimento; Declaração de Helsinki*

Persons engaged in research involving human subjects know that such work involves a paradox. To be ethical, the investigator must treat his subjects as autonomous persons, possessed of free will and an impressive set of moral rights (National Commission for the Protection of Human Subjects of Bioethical and Behavioral Research, 1978). To be professional, the investigator must treat his subjects as scientific objects, subject to the laws of nature and the impersonal rules of cause and effect (Jonas, 1975). Kant argued long ago that people should not be treated like objects. But research involving human beings seems to require just that.

For many years, this paradox was a burden for researchers, left for researchers to resolve. Though the degradation of medical research under the Nazis produced the Nuremberg Code in 1947 (Anonymous, 1949), for the conduct of clinical research the rules of this code were to be enforced by scientists, not governments. But a series of research scandals in the 1960s in the United States undermined public confidence that the research community could police itself (Faden et al., 1986). In the confused politics of the day, distrust of government combined with calls for increased government regulation. The paradise of self-regulation ended in 1974 with the installation of the current US system of research regulations (NIH, 2001).

The current US system combines review of research by local ethics committees (IRBs) with Multiple Project Assurances (MPAs) provided by research institutions to Washington that they will conduct all research in accord with government regulations, i.e., to receive money for one project they must pledge to conform to rule in all the rest. Despite complaints, the system functioned well through the 1970s and 80s.

But in the 1990s, accusations arose in the United States that the system failed to properly regulate US research conducted in developing countries. In particular, it was argued that several placebo-controlled studies of the "short course" of AZT for the prevention of vertical transmission of HIV were unethical and could never have been conducted within the borders of the United States (Angell, 1997). American scientists conducting research in developing counties found themselves the targets of a media frenzy, which combined general doubts about the ethics of human research with particular suspicions about the intentions of corporations that sponsored research in developing countries. In 1999 President Clinton directed the National Bioethics Advisory Commission (NBAC) to look into the problem and make recommendations. At the same time, ethics activists within the World Medical Association (WMA) began a campaign for changes in the WMA "Declaration of Helsinki" that would block future studies along the lines of the "short course" AZT trials. The Declaration of Helsinki was revised in October 2000 (WMA, 2000); the NBAC presented its report in April of 2001 (NBAC, 2001).

The discussions that prompted these changes and recommendations were, in my view, largely incoherent.

Critics of the short course of AZT trials argued that if the researchers had acted differently, for example, if they had provided all pregnant women with a long course of AZT, fewer children in the world would have been born with HIV. Since deliberately allowing the infection of children is immoral, the studies were immoral (Lurie & Wolfe, 1997).

But this "infected children" argument is logically unsound. Although it is true that if the researchers had acted differently, fewer children would have been born with HIV, it is also true that fewer children would have been born in the world with HIV if you, the reader of this article, had donated all your savings to Médecins Sans Frontières or similar groups struggling for public health in developing countries. The moral problem for research is not whether, if the researchers had acted differently, the world would be a better place. That is a problem for all of us. The particular moral problem in research is whether the researchers engaged in coercion, deception, or exploitation of their subjects, and this, the evidence shows, they did not do (Lackey, 2001).

Instead of responding in these terms, researchers who supported the AZT trials and similar placebo-controlled studies argued (unfortunately) that no harm had been done to subjects in these trials because the subjects were no worse off than they would have been if the study had never been conducted in the first place. After all (they said), even subjects in the placebo arm, receiving no treatment, were being supplied with the "prevailing standard of care," since the standard of care in the circumstances of poverty is no treatment at all (Varmus & Satcher, 1997). If this "standard of care" argument were sound, it would justify me in walking past a child drowning in a river and not throwing him a lifeline, on the grounds that, even if I do not throw the lifeline, the child is no worse off than he would have been if I had never walked by. Since it is patently immoral for me to ignore a drowning child, the "standard of care" argument must be unsound. Nor could I morally justify my refusal to throw the

lifeline on the grounds that it is not the custom in that country to rescue drowning people.

Given the confusions in logic on both sides of the controversy, it is not surprising that ensuing policy changes were unfortunate.

Revision of the Declaration of Helsinki

Before October 2000, the Declaration of Helsinki (II.3) read: "*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*".

The old rule II.3 rule permits the use of a placebo arm in clinical trials provided that the investigator can certify that the therapy in the active arm is not known to be superior. People in the placebo group receive no therapy, but the moral difficulty of this was presumably removed by the consent process, which informs all subjects of the existence of the placebo arm and the possibility of placement in it.

In the 1990s the question was repeatedly raised whether the consent process could bear this burden, especially if the trial were conducted in a developing country, where subjects are often poor, illiterate, desperately ill, and completely ignorant of the design of placebo-controlled trials (Del Rio, 1998). It was argued that such subjects do not know what they are consenting to, and that in particular they do not know that they are consenting to a process in which they may receive no treatment when proven treatments do exist. The short course AZT trials were cited as examples where the informed consent process has failed and harm to subjects had ensued. In response to these arguments, the Declaration was changed to "*Principle 29: 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*".

It is clear after this revision that the number of permissible placebo-controlled trials will be small indeed. The vast majority of acceptable studies by this rule must have two active arms, comparing proven treatment with unproven treatment (Koski, 2001).

Criticisms of the revision

The arguments for revising the Declaration of Helsinki had two components. One component argued that the informed consent process did not work in developed countries. The second was that placebo controlled studies wrongfully expose subjects to risk and harm. Both arguments were misguided.

The argument that the informed consent process does not work in developing countries presumes that subjects in developing countries have a harder time understanding consent forms than subjects in developed countries. But studies show that subjects in developed countries have their own difficulties understanding consent forms (Daugherty et al., 1997). No one has demonstrated that the percentage of uncomprehending subjects is higher, *ceteris paribus*, in developing countries than in developed ones. To argue, absent evidence, that subjects in developing countries are less able to comprehend consent forms and the consent process is to invoke paternalism and colonialism. The very activists who deride consent forms in developing countries are the first to insist on the primacy of the consent forms in developed countries. To avoid colonialism, we must believe that the consent process, properly administered, can work in developing countries. Subjects in developing countries should be protected, but not from their own informed consent.

The argument that placebo-controlled trials wrongfully harm subjects neglects the fact that in numerous cases the placebo-controlled trial will yield statistically significant results in less time and with fewer subjects than a trial with two active arms. Thus if an ineffective therapy is tested in a placebo-controlled trial, all subjects learn sooner that the therapy does not work and can move on to try new things. Furthermore, if the therapy has significant side effects, fewer subjects will be exposed to these side effects in a placebo-controlled trial than a trial with active controls. It follows that in many cases fewer subjects will be harmed in a placebo-controlled trial than in a trial with active controls (Emmanuel & Miller, 2001). In sum, the choice between a placebo-controlled trial and the trial with two active arms is not a moral choice. It is a scientific choice, and should be based on a careful study of empirical factors indicating how knowledge is best obtained. To have a blanket moral rule banning placebo controls protects no one and blocks scientific progress.

Another difficulty with the new Declaration of Helsinki is that it forbids all studies of the comparative cost-effectiveness of drugs. Suppose that there are two drugs A and B known to be effective against a certain condition C, that B is one-tenth as expensive than A, that B is

known to be less effective than A, but that it is not known precisely how much less effective B is. In a country with limited public health resources, it may be important to know whether B is one-half, or one-tenth, or one-hundredth as effective as A, so that purchases of A and B can be adjusted for maximum per-dollar effectiveness across the population. But the Helsinki Declaration, as now worded, would forbid a trial in which one arm tested B. Apparently the attempt to protect developing countries from depredation by their rich neighbors has produced an ethical imperialism in which the concerns of medical ethics in rich countries are projected onto poor societies whose vital interests lie elsewhere (Shapiro & Meslin, 2001).

The National Bioethics Advisory Commission: basic recommendations

The recommendations of the National Bioethics Advisory Commission (NBAC, 2001a) do not have the quasi-legal status of the Declaration of Helsinki. Nevertheless the report issued by the NBAC in April 2001 contains the most thorough attempt to date to deal with the complexities of research in developing countries, and represents the combined efforts of hundreds of witnesses and consultants to develop a consensus on the issues. The primary recommendation of the NBAC (1.1) is that roughly same protections afforded to subjects in the United States must be provided to all subjects in international trials sponsored or conducted by the American government. These include: (a) *prior review by an ethics committee*, (b) *minimizing of risks*, (c) *reasonable balance of risks against benefits*, (d) *compensation for injuries directly sustained during research*, (e) *individual informed consent for all participants*, (f) *equal rights for all participants*, and (g) *equitable distribution of the benefits and burdens of research*.

To assure that these protections are extended to subjects in studies sponsored by drug companies and other nongovernmental organizations, the commission recommends that (1.2) "*The [US] Food and Drug administration not accept data obtained from clinical trials that do not meet the substantive ethical protections outlined in Recommendation 1.1*".

Most of these recommendations flow deductively from the concepts of ethics and moral prudence: protecting rights, minimizing risks, and so forth. Some of them, like the "ethics committee" requirement, reflect hard-won US experience. On the other hand the requirement (d) of "compensation for injury" provides a protection that goes beyond that afforded by regulation to US subjects in domestic trials (US subjects can expect immediate medical aid if injured in trials, and can sue for negligence, but have no right to compensation for injuries not caused by negligence). The inclusion of this extraordinary provision (d) is perhaps motivated by the thought that subjects in developing countries have little chance of success in lawsuits against multinational companies. Nevertheless, it would be surprising and perhaps unfortunate if the FDA refused to accept data regarding (say) a promising AIDS vaccine on the grounds that the drug company conducting the trials had failed to provide compensation to consenting subjects who suffered from idiosyncratic and unforeseeable injuries during the course of vaccine trials.

The fear of exploitation marks the third NBAC recommendation (1.3): "*Clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country*".

One can sympathize with the frustration of public health authorities in developing countries, who see 90% of the world's clinical research dollars spent on medical problems that afflict only 10% of the world's population (NBAC, 2001b). If in country A there is *a*'s disease and in country B there is *b*'s disease, it is better that *a* be studied in A and *b* be studied in B. But what if the only choice is between having a study of *b* in A and having no study in A at all? Subjects in studies frequently receive medical work-ups and obtain medical care as participants that they might never receive if there were no study at all. And the medical authorities in A can benefit from a study of *b* in A by participating and learning the basic skills for the conduct of clinical trials; indeed, development of local research skill is a priority recommendation of the NBAC (5.6; 5.7). These benefits would be lost by a rigid application of recommendation 1.3.

The NBAC on placebo controls

The arguments about "the victims on placebo" that caused the revision of the Declaration of Helsinki were presented to the NBAC. On this issue the NBAC bent but did not break: (2.2) "*Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such a treatment is available in the host country. Any study that would not provide the control group with an established effec-*

tive treatment should include a justification for using an alternative design".

Recommendation 2.2 does not argue that placebo controls are always immoral when an effective treatment exists, nor does it instruct ethics committees to systematically reject placebo-controlled studies. It places a burden of explanation on researchers to justify the use of placebo controls when active controls are possible. Since every research design is subject to moral scrutiny by IRBs, this is not an undue burden. 2.2 is what the Declaration of Helsinki should have become, in response to the controversies of the 1990s.

The NBAC on informed consent

The NBAC affirms the basic principle of individual voluntary informed consent for international as well as domestic studies (3.1). Various concessions to cultural differences appear subsequent to 3.1. The Commission conceded that on occasion a husband's consent might be necessary if a wife is to participate (3.6; 3.9), or that a tribal leader's consent might be necessary for a tribal member to participate (3.8). In such cases, however, the consent of the husband and the consent of the tribal leader must supervene on the informed and independent consent from the actual participant.

How this will play out psychologically in the field is unclear. Presumably if the husband and wife walk in together they have discussed the matter before showing up, and the views of the psychologically stronger spouse will prevail. But now suppose that a husband or tribal leader has "had a talk" with some person and that this talk has created some pressure to participate. Now the researcher comes along and signs the subject up. Even if the husband or tribal leader has exercised coercion, the researcher has not. To what extent are researchers to blame; to what extent should their research be disrupted, due to coercion exerted by people other than themselves?

The NBAC's sensitivity to prevailing cultural norms (relative to the WMA) led to recommendation 3.11. "*US research regulations should be amended to permit ethics review committees to waive the requirements for written and signed consent documents in accordance with local cultural norms*".

Of course this proviso is more "political" than "cultural": forms that indicated a personal connection to American organizations were a death warrant in Cambodia in 1975, and similar jeopardy for subjects may arise after fundamentalist coups of various sorts. It would have been interesting for the commission to require researchers to prepare plans for the quick shredding of signed documents that remain in storage in host countries that are politically unstable.

NBAC on post-trial benefits to subjects

The NBAC paid particular attention to the problem of post-trial benefits (4.1): "*Researchers and sponsors in clinical trials should make reasonable good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants*".

Surely it would be nice for researchers to do this, but is this supererogatory (praiseworthy when done but not blameworthy when not done) or is it morally required? Suppose that there is some serious condition and that a subject in a trial benefits from the experimental treatment. The trial ends, the treatment is stopped, the subject's medical problem emerges from remission. Has the researcher done the subject wrong? Not only is the subject no worse than he would have been if there had been no trial; he is in fact much better off. If no promise was made to continue therapy past a certain point, how can a researcher be said to have wronged the subject? Continued treatment, then, is an act of compassion. Now compassion is a good thing, but compassion, like love, is not something that can be commanded by moral codes. When we speak of compassion we speak not of moral requirements but counsels of perfection. This is especially true in the research setting, where the goal of the activity is truth, not the solution of personal health problems.

Though "open label" phases of studies frequently follow upon double-blind clinical trials in the United States, there is no requirement, in domestic American studies, that subjects be provided with continuing effective therapy after a trial is concluded The commission's recommendation 4.1 goes beyond American requirements, and no argument is provided that subjects in developing countries have some special need for continued treatment that domestic subjects do not have.

The NBAC on post-trial distribution in the host nation

The NBAC backed off on the requirement that sponsors of successful studies ensure that citi-

zens at large in the host nation will have access to newly proven therapies. Researchers are simply required to consider the issue (4.2): "*Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves... In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee why the research is nonetheless responsive to the health needs of the country*".

One could well imagine the consternation of organizations and corporations saddled with an open-ended requirement to supply, perhaps free of charge, the results of their successful clinical trials. The NBAC did well to reject any such suggestion. But it is disappointing that the NBAC in its inquiry into this subject devoted its attention to clinical investigators and their responsibilities rather than to the government they are charged to advise. The arrival of AIDS, resistant infections, West Nile viruses, and other unwelcome visitors have made even the average US citizen realize that public health problems in foreign countries have a direct bearing on his own health. The United States has the option of developing new programs of grants and loans to enable developing countries to obtain supplies of new drugs and vaccines without denying nongovernmental organizations and corporations the fruits of their own endeavors. The legal mechanisms which have enabled governments in developing countries to purchase weapons on the American tab could and should be converted into mechanisms for the purchase of medicines. To assure that this is done, however, is the responsibility of American citizens and their representatives: it is not a burden that falls alone on those who do research.

Discussion

The controversial studies of the 1990s produced a response in the direction of increased regulation. The new regulations focused on study design, with intense suspicion directed towards placebo-controlled studies and the processes of informed consent. The resulting revision of the Declaration of Helsinki must be viewed as a major setback for clinical research in developing countries. The recommendations of the NBAC are more judicious, but suffer from a failure to distinguish counsels of perfection from basic moral requirements.

One senses reading the NBAC report that a major opportunity to survey this problem from the ground up has been missed. In moral matters, as in practical life, it is more important to worry about avoiding disaster than achieving perfection. If we ask, what is perfection in clinical research settings? The answer is: perfectly voluntary and perfectly informed consent. But that is an objective that we will never reach. If we ask, what moral disaster do we wish to avoid in clinical research? the answer is: coercive, deceptive, and exploitative acts by researchers. Much of the discussion in the WMA and the NBAC is concerned with voluntary informed consent: it is focused on the minds of the subjects, which are often opaque. Very little discussion is devoted to the elimination of coercion, deception, and exploitation, which is found in the overt actions of researchers, and can be identified without mental telepathy. Had the NBAC concentrated on the character of researchers, rather than the minds of subjects, their report would have been different, and perhaps more useful, than what we have.

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