Ethical issues in clinical trial collaborations with developing countries - with special reference to preventive HIV vaccine trials with secondary endpoints

Reidar K. Lie, M.D., Ph.D.
Department of Philosophy
University of Bergen
Sydnesplassen 7
N-5007 Bergen, Norway

Fax. + 47 55 58 96 51
Tel. + 47 55 58 24 37

Email: Reidar.Lie@fil.uib.no

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1. INTRODUCTION

Existing research ethics guidelines

One central ethical concern when conducting research on human subjects which involves a collaboration between research groups in different countries is to avoid research which has been rejected as unethical in one of the countries. It is not difficult to point to examples of such research in the past (Kiatboonsri & Richter, 1988). In order to ensure that cases such as these do not happen, it has become generally accepted that collaborative research should be approved by the relevant bodies (regulatory authorities, ethics committees) in both countries (see CIOMS guideline 15) . If the research protocol is rejected in one country, the research should not be carried out.

Some of the wording in the CIOMS guidelines represents a stronger version of this principle. Fundamental to the CIOMS guidelines is the notion that some groups or countries are more vulnerable than others and need special protection. A vulnerable group could be an underdeveloped community in a developed or a developing country, or could be a developing country in relation to a developed country. According to these guidelines, if research can be carried out in the developed community, then it should not be carried out at all in an underdeveloped community. If the research needs to be carried out in an underdeveloped community, not only should it be approved in both places, but it actually needs to be carried out in both places simultaneously. This is reflected in the following guideline 8:

> Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably in developed communities.

In the commentary to this guideline, it is stated even more precisely:

> Phase I drug studies and Phase I and II vaccine studies should be conducted only in developed communities of the country of the sponsor. In general, phase III vaccine trials and phase II and III drug trials should be conducted simultaneously in the host community and the sponsoring country; they may be omitted in the sponsoring country on condition only that the drug or vaccine is designed to treat or prevent a disease or other condition that rarely or never occurs in the sponsoring country.

It is not difficult to see the attraction of wanting to adhere to such a principle. By following this principle, one would not only avoid the obvious cases of abuse, but, by requiring that the sponsoring country actually carries out the research at home, one would ensure that there are no reasons which may not be immediately obvious to outsiders for not wanting to carry out the research in one's home country.

The principle has received widespread support from some developing countries and from a number of commentators. The Indian Council of Medical Research recently refused to fund

research by foreign organizations if they are only carried out in India (Mudur, 1997). The National HIV/AIDS Vaccine Trial and Evaluation Plan of Thailand required that preventive HIV vaccine candidates should be tested in the sponsoring country before phase I/II trials are initiated in Thailand, in agreement with the CIOMS guidelines, although this policy has recently been changed (see below). The same is the case with the guidelines approved by the Brazilian AIDS Vaccine Committee (Greco, 1997).

Some commentators have expressed a general distrust in the intentions of foreign scientists wishing to do research in developing countries, because of past examples of abuse (Gbolade, 1997). Garner et al for example have pointed out that researchers sometimes conduct a trial in a developing country, build the necessary infrastructure to do the research, but then when the research has been carried out and shown a positive effect of an intervention, leave the country behind without any benefits at all (Garner et al., 1994). If the research is carried out in this way is of primary benefit to the sponsoring country, and in addition is regarded to be unethical in that country, it is a particularly blatant example of exploitation of developing countries. One of the primary motivations behind the CIOMS guidelines is to avoid such cases of exploitation and abuse, which is reflected in the following subsection of guideline 8:

> the research is responsive to the health needs and the priorities of the community in which it is to be carried out

And in the commentary to this guideline, as well as in the commentary to guideline 15, it is stated:

> As a general rule, the sponsoring agent should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research is carried out; exceptions to this general requirement should be justified and agreed to by all concerned parties before the research is begun.

Relevant to the issue of the ethics of collaborative research are also some passages from the Declaration of Helsinki (latest version, October 1996):

> I.5. Concern for the interests of the subjects must always prevail over the interests of science and society
>
> 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. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exits.
>
> II.6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value to the patient.

These principles of the Helsinki declaration are also endorsed by the CIOMS guidelines. The commentary to guideline 14 states that the ethical review committee must ensure that "the provisions of the Declaration of Helsinki are applied in all biomedical research involving human subjects.". Furthermore, the commentary of this guideline 14 quotes section II.3 of the Helsinki declaration, and adds that "if there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified". It continues, "no other interventions must be known to be superior to those being compared in the clinical trial, unless eligibility to participate is limited to persons who have been unsuccessfully treated with the other superior intervention or to persons who are aware of the other intervention and its superiority and have chosen not to accept it".

Principle I.5 of the Helsinki declaration seems to say that one cannot justify endangering individuals for the sake of acquiring knowledge that may benefit society in general or future patients. The reason for wanting to accept such a principle is obviously to avoid repeating the past examples of misuse of research where dangerous research projects were justified for precisely this reason. The principle is, however, problematic, if, as some have argued, all clinical trials involve a certain amount of risk for the research subjects which is justified in terms of possible future benefit (I have discussed this elsewhere Lie, In press, and see below). The Helsinki declaration explicitly demands that participants in clinical trials should receive the best proven therapy. Neither the Helsinki declaration nor the CIOMS guidelines refer to restrictions on this principle because of different circumstances. Language such as "there is .. an approved ... drug" and "no other interventions must be known to be superior" does not place limits on what should be provided to what is common practice in the place where the trial is conducted, although this interpretation may not in fact be what is intended by those who wrote the guidelines. It is this principle which seems to be violated in some of the recent controversial clinical trials.

The issue of HIV vaccine efficacy trials with secondary endpoints

A number of recent cases have raised the issue of the appropriateness of the guidelines. One such case is HIV vaccine trials with secondary endpoints. The ethical dilemma with regard to HIV vaccine trials with secondary endpoints is the following. An effective preventive AIDS vaccine need not only prevent infection, a primary endpoint, but could also be of value if it modified disease progression, a secondary endpoint. It would for example be of interest to see if a vaccine, although it did not prevent infection, reduced a person's viral load. A reduced viral load would be associated with a better prognosis. This way of making a distinction between primary and secondary endpoints may not be the way it is usually done, but it follows the way the distinction is drawn in UNAIDS documents on this matter. If standard therapy in industrialized nations, however, is to treat patients immediately following infection with currently available combinations of drugs that are highly effective in reducing viral load, it would be impossible to carry out such secondary endpoint trials in these countries. Such trials could of course be carried out in countries where the drug therapies are not available for economic reasons. If, however, as the guidelines mentioned above seem to require, trials have to be carried out simultaneously in both host and sponsoring country, all participants have to receive the best proven therapy, then these trials

cannot be carried out in any country. The consequence of this would be that it is impossible to find out whether a vaccine candidate is effective with regard to secondary endpoints and whether it could possibly save a large number of lives.

This particular case is not the only one, and it raises the more general question under what circumstances, if any, is it ethical to conduct a study in one country that cannot be ethically conducted in another. This background paper will examine that question. I will do so by examining the current guidelines in relation to a number of recent cases that have shown that the guidelines need revision. I will also discuss the recent controversy over the perinatal transmission studies as we can draw some important lessons from this controversy. Based on this discussion, I will return to the issue of HIV vaccine trials with secondary endpoints.

2. PROBLEMS WITH THE GUIDELINES

Although, as has been mentioned above, there are obvious reasons why one would want to adhere to the existing guidelines, a number of recent cases have indicated that some of the wording may need modification. There are basically five issues that need discussion:

- The notion of 'underdeveloped communities' that are 'vulnerable' and may need special protection
- What one should do when there is legitimate disagreement among experts concerning the possible benefits of a particular treatment
- The relevance of different evaluations of risks versus benefit because a particular disease is a much greater problem in one country, or the urgency of developing a treatment is much higher
- The appropriateness of the general prohibition against carrying out phase III trials in developing countries but not in developed countries
- How one should deal with the fact that, because of economic conditions, some treatments are not available in one country, but available in another country

In this section I shall discuss the first four issues as they are the easiest to deal with. I shall argue that one should reject a general notion of 'underdeveloped communities'; that one can carry out a trial in one country that is not carried out in another if the reason for this is genuine disagreements among experts; that one should be skeptical about justifying trials in one country because of different risk-benefit evaluations; and that the general prohibition against carrying out phase III trials in developing countries is not defensible. I shall in the next major session examine the issue of different economic conditions.

The CIOMS notion of "Underdeveloped communities"

The CIOMS guidelines introduces the notion of an "underdeveloped community" that needs special protection because it is vulnerable to exploitation. There is a long tradition in research

ethics for identifying certain populations as vulnerable, such as prisoners, children or psychiatric patients. Special care needs to be taken when doing research among these populations. For example, it is a generally accepted principle that one should not do research on children that can just as well be done on adults. In the CIOMS declaration this is reflected in the notion that one should not do research in 'underdeveloped communities' if that research can be done elsewhere. Specifically, this means that one should not do phase I and phase II vaccine studies in 'underdeveloped communities'. The rationale for this is, that since phase I and phase II studies are designed to test safety and immunogenicity, and there is not reason to expect that this would differ among different populations, there is no need to do these studies in underdeveloped communities.

The notion of 'underdeveloped communities' differs from other types of populations, such as prisoners, children, and psychiatric patients. It is relatively ease to give precise criteria for who belongs to these populations, but this is not the case for what should count as an underdeveloped community. Clearly it has to be a relative term. Communities may be 'underdeveloped' in one sense, such as economically, and developed in another sense, such as having a well functioning research review procedure. It would for example be wrong to lump all those countries together who are called 'developing countries' in an economic sense and identify them as 'underdeveloped' for research ethics purposes. For this reason, it might be preferable to drop this term altogether, and concentrate on principles that should govern all collaborative research between countries where conditions differ. This may be differences in economic conditions, it may be differences in research ethics review procedures, and it may be differences in basic values. If this approach is taken, one would have to evaluate each situation separately and ask if a particular research project can be carried out in one country if it is not carried out in another country.

This recommendation to drop the general term 'underdeveloped communities' should, however, not mean that some of the substantial reasons for wanting to adopt such a term are rejected. There is a real issue of wanting to avoid exploitation of one group by a more powerful group. My scepticism against the term 'underdeveloped communities' merely questions whether this term is the best to capture our desire of wanting to identify situations where exploitations are likely to occur.

Different opinions among experts

Several recent cases have shown that there is another reason why the general prohibition of carrying out trials in one a host country, but not in the sponsoring country, is problematic. These are cases where there are genuine differences of opinions among experts about what should be regarded as standard of care.

The first example is the tuberculosis case mentioned by Marcia Angell in her recent editorial commented on more fully below (Angell, 1997b). In Uganda a clinical trial was carried out to ascertain the effects of various regimens of prophylaxis against tuberculosis among HIV positive adults. One group in the trial received a placebo. Angell makes the point that this trial could not have been carried out in the US, as various advisory bodies had previously issued recommendations that all HIV positive persons with a positive tuberculin test should receive

preventive therapy (Msamanga & Fawzi, 1997; Whalen et al., 1997). Angell also notes, however, that there was no universal agreement as to whether this recommendation should constitute standard of care. She concedes that under these circumstances a trial that could not have been carried out in the US, nevertheless can be justifiably carried out in another country.

If this is accepted, we admit of an exception to the CIOMS rules in cases where there are legitimate differences of opinion about what constitutes standard of care. I have elsewhere discussed two similar cases: the decision of WHO to go ahead with trials of preventive AIDS vaccines in developing countries despite the decision by US authorities to put these trials on hold, and the acellular pertussis vaccine trials in Sweden (Lie, Forthcoming). In both of these cases I think a case can be made that there are legitimate disagreements among experts, although I believe a stronger case can be made for legitimate disagreements in the HIV vaccine case compared with the pertussis case. After all, the US decision concerning HIV vaccine trials was controversial even among US experts, whereas a vast majority of experts would agree that the Swedish and Italian pertussis vaccination policies could not be defended as standard of care.

One should, however, note that these cases are not in violation of the principles of the Helsinki declaration. The Helsinki declaration demands that all participants should receive the best proven therapy; if there is disagreement among experts there simply is no single best proven therapy. Even in cases of disagreements about standards of care, however, there may be agreement among experts that some other treatments are inferior. In such cases, although one cannot identify one unique treatment, one can rule out those treatments considered inferior by all experts. The situation where there is disagreements among experts about what is the best therapy, is precisely the situation where there is clinical equipoise, and when the initiation of clinical trials can be justified.

The notion of different levels of risk in different countries

A common argument in the discussion about the ethics of collaborative research is that different levels of risk in different countries may mean that a trial that cannot justifiably carried out in one country, nevertheless can be carried out in another. For example, it is pointed out that AIDS is much bigger problem in many developing countries; therefore it may be ethically acceptable to carry out trials in these countries which may not be acceptable in industrialized nations where the AIDS problem is much less of a problem. Often when this argument is presented one simply points to the number of AIDS cases in different countries, and leaves the rest of the risk-benefit calculation unspecified. Let us therefore try to flesh out the argument.

The benefit we are talking about here is benefit to society, or benefit to future vaccine recipients. For an excellent discussion of the various types of benefits and risks in clinical trials, see (Levine, 1986). If an effective vaccine is developed, people in the future would have access to this vaccine and avoid infection. In developing countries a much larger population is at risk of infection; therefore the potential benefits of an effective vaccine is much greater in developing countries. There are also some ‘societal’ risks: if the vaccine turns out to be ineffective, resources will have been wasted, or a general scepticism towards the development of new vaccines may arise in the country where the trial has taken place. Clearly, different countries may make different

judgements with regard to how to balance these types of risks against the possible benefits of a vaccine candidate, and may legitimately reach different conclusions depending on how much of a health problem AIDS is in the country. One country may for example conclude that the expense of a phase III trial is justified in light of current science because of the expected benefits if the vaccine turns out to be effective, whereas another country may decide that the expenses are not justified. If this is what is meant by different levels of risks in different countries, a case can be made for carrying out a trial in one country, but not in another.

There may, however, also be risks to the participants, such as possible side-effects of the vaccine, social discrimination as a result of taking part in the vaccine trial, or the possibility that future, more effective vaccines, will not be as effective to the trial participants. One might be tempted to weigh these types of risks against the possible benefits, and then also conclude that one may accept a higher level of these individual risks in a country where the potential benefits of a vaccine are greater. The problem with this position is that it seems to violate the Declaration of Helsinki's principle I.5: Concern for the interests of the subjects must always prevail over the interests of science and society. If the reason for wanting to carry out a trial in one country, but not another, is that the benefits to society is much greater in the first country, then it would seem that the interests of society do prevail over the interests of the subjects.

There is a line of argument, however, that, if valid, would entail that under some circumstances it would nevertheless be justifiable to carry out trials in one country on the basis of an estimate of the individual risk vs. societal benefit ratio. This line of argument does, however, depend on what is currently a controversial position among commentators on research ethics. For a discussion see (Lie, In press). Many, including, Benjamin Freedman, have argued that one should never admit arguments in terms of individual risks vs. societal benefits:

> Proponents of clinical trials ... often ... argue that there is a need to balance the rights of subjects against the needs of society. By this tactic, the proponents of clinical trials have implicitly surrendered, for to admit that something is a right is to admit that it represents a domain of action protected from the claims and interests of other individuals or of society itself"(Freedman, 1992).

Others such as Robert Levine has at least voiced caution when weighing benefits to society versus risks to research subjects (Levine, 1986, p. 62). Still others have pointed out that all clinical trials assume some type of altruistic motive among trial participants, and that one will always have to weigh the possible risks to the participants against the possible benefit to society. This means that it is never possible to fulfill a strict interpretation of principle I.5 of the Helsinki-declaration in any country. An ethics committee has the obligation to weigh these individual risks against the possible benefits to society, but in addition there has to be a real disclosure of the inherent risks in the research proposal. Each potential trial participant has to decide for himself or herself whether the possible individual risks are outweighed by the possible benefits to future patients, and then decide if he or she wants to take part in the trial on the basis of a motive of wanting to assume these individual risks for the possible benefit of future patients. If that is the case, it is again reasonable to expect that different people may evaluate these types of risk vs. benefits differently, both as members of regulatory committees and as individual potential trial participants. If one

wishes to use this argument, one should recognize its controversial nature, and recognize that it depends on an informed consent process that is probably never realized in most trials in any country. Margaret A. Somerville has emphasized the problems of proper informed consent in this context (Somerville, 1997). Finally, in the context of HIV vaccine trials, investigators involved in these trials, such as Dirceu B. Greco, have also warned against accepting a higher individual risk for participants in these trials with the justification that there will be a greater social benefit in developing countries: "The consideration that 'the AIDS epidemic is out of control, that the preventive measures do not work and that any vaccine independent of its efficacy is better than nothing' may put out of focus all the reasonable ethical and scientific evaluations, especially when we know that much of the knowledge needed is still lacking"(Greco, 1997).

Previous trials in developing countries

The discussion above indicates that there is a problem with a general prohibition against carrying out phase III trials in developing countries but not in developed countries. An examination of a number of previous trials in developing countries further supports this position.

During the May 8th Congressional hearings, CDC's David Satcher emphasized the principle of the CIOMS guidelines that requires research to meet the needs and interests of the host country and is going to result in benefits for the host country. As an example of such research he mentioned the hepatitis B studies that were done in China in the early 1980s. The studies on oral rehydration therapy for Cholera in Bangladesh were also mentioned as examples of such research. It may be instructive to examine these examples.

In the mid 1960s standard treatment of cholera was replacement of lost water and electrolytes by intravenous fluids, which was a highly effective treatment. This treatment could not be used as a widely available treatment in developing countries, for both economic and logistic reasons, and it would be desirable to study alternative treatments more suitable to the conditions in developing countries. One such alternative treatment was to give electrolyte solutions by mouth. We now of course know that oral rehydration has saved hundreds of thousands of lives. The situation at the end of the 1960s with regard to treatment of diarrhea in developing countries is therefore very similar to the current situation with regard to prevention of HIV transmission.

Studies published in 1968 had shown that cholera patients did absorb fluids infused to their stomachs (see for example Hirschhorn et al., 1968; Pierce et al., 1968). In 1968-1969 several clinical trials were published showing that oral rehydration was just as effective as treatment for cholera. Interestingly enough these are not placebo controlled trials. The control groups received the then standard therapy of intravenous fluids. This is the case both for the two studies carried out in Calcutta, India (Pierce et al., 1969; Sack et al., 1970), and the one in Dacca, Bangladesh (then East Pakistan) (Nalin et al., 1968).

Mabey et al (1996) mentions several trials carried out in developing countries which have changed therapies. One is a trial showing that chloramphenicol is effective against meningitis (Whittle et al., 1973). The standard treatment was intramuscular penicillin, which was also not used much in the area because for reasons of economics and logistics. In this trial also, the newly

proposed treatment, chloramphenicol, was tested not against placebo, but against penicillin. Another trial is a trial of a shorter course of treatment for tuberculosis (East African/British Medical Research Council, 1972). The justification for initiation of this trial was again that the longer, standard treatment, was difficult to implement, although the main argument was not economic in this case. This trial also used standard therapy as the control group. Finally, a trial in Tanzania showed that management of sexually transmitted diseases significantly reduced HIV incidence in a population (Grosskurth et al., 1995). This was a randomized controlled study where six communities were randomized to an intervention group and six to a control group, receiving no intervention. The authors justify their study by stating that "no empirical data have been available on the impact of such measures [STD control] on the incidence of HIV-infection".

Several interesting things emerge from these cases. First, when there is an effective treatment, such as intravenous fluids for diarrhea or penicillin for meningitis, the control groups receive that treatment, although it is not generally available in the country and is too expensive for widespread use. I shall return to this point below. Second, when there is absence of empirical data about effectiveness, as in the case of the STD study in Tanzania or the treatment of tuberculosis in Uganda mentioned earlier, there is a placebo group. Third, these are all trials that were carried out in developing countries, but not in developed countries, and involved a collaboration between researchers in a developed and a developing country. I believe very few, if any, would label these trials unethical. Examples such as these therefore show the unreasonableness of requiring that phase III trials have to be carried out simultaneously in the two countries involved.

Finally, let us examine the hepatitis B vaccine trials in China. This case shows how some researchers advocated placebo controlled trials, whereas other researchers did not. One suspects that general attitudes towards the necessity of carrying out placebo controlled trials determine the particular decision made by the different researchers (more on this below). Hepatitis B is endemic in many Asian countries, and many are infected during birth and childhood. An effective vaccine against hepatitis B was introduced around 1980. At that time it was not known whether this vaccine would be effective against perinatal transmission. An alternative treatment would be to give hepatitis-B immunoglobulin to newborn babies of mothers who are carries of HbeAg. This is, however, a very expensive treatment, and there was a great interest in developing a cheaper alternative, such as routine hepatitis B vaccination at birth. Several trials established that such routine vaccination was indeed effective (Lo et al., 1985; Wong et al., 1984; Xu et al., 1985). The two first trials were randomized using a placebo control group, whereas the last one in Taiwan used as controls those who refused vaccination. A fourth trial recruited patients in Taiwan between February 1982 and December 1983 using a non-randomized control group who did not receive vaccination (Lieming et al., 1993).

Let us first examine the justification for the initiation of the trial by Wong et al. This trial was started in Hong Kong in June 1981 with the collaboration of Dutch researchers, and at that time nothing was known about the effectiveness of hepatitis B vaccine when given immediately after birth, although a study was published in February of that year, showing a positive effect on children in Senegal. In this study randomization was done by village (Maupas et al., 1981). One could thus argue that at the time of the initiation of this trial there was not sufficient knowledge in order to reach a firm conclusion. Interestingly, this trial was cut short earlier than planned, in September 1983, when the investigators learned of a result of a clinical trial showing that

immunoglobulin was effective (Beasley et al., 1983). At that time they did not feel justified in continuing with a placebo group. One should also mention that an earlier report from the same study had already indicated the effectiveness of immunoglobulin in preventing hepatitis B infection (Beasley et al., 1981). This is reflected in various recommendations in the period from 1981-1982 from CDC and the American Academy of Pediatrics to give HBIG to infants of all HbsAG positive mothers (Chin, 1983) and the fact that in Italy two studies were carried out not using placebo, but immunoglobulin in the control group (Scaravelli et al., 1984) (Piazza et al., 1985). Nevertheless, one could concede that until the trial by Beasley was published in 1983 it was not firmly established that immunoglobulin was effective. At that time the investigators in the Wong et al trial decided it was unethical to continue with a placebo group. However, the US sponsored trial in China continued to recruit patients to placebo until the end of February 1984. Taiwan initiated already in July 1984 a nationwide vaccination program with immunoglobulin and HBV vaccine for high-risk infants (Lo et al., 1985).

The CIOMS guidelines also prohibit carrying out phase I and phase II trials in developing countries. The recent discussion about the justifiability of carrying out certain phase I and II vaccine trials in Thailand shows the problematic nature of this general prohibition. The National HIV/AIDS Vaccine Trial and Evaluation Plan of Thailand required that preventive HIV vaccine candidates should be tested in the host country before phase I/II trials are initiated in Thailand. This, of course, is in agreement with the CIOMS guidelines. Some of the candidate vaccines undergoing testing in Thailand are directed against the subtype B of the virus, common in the US, and these vaccine candidates have undergone testing in the US before trials started in Thailand. A common criticism against these trials have been that the vaccine candidates are not directed against the common subtype in Thailand, subtype E. Recently the US based company Biocine has developed a vaccine based on subtype E, and plans are underway to start phase I/II trials in Thailand. This particular vaccine type has, however, not previously been tested in the US. This has created a discussion about whether this is permissible (Bhatiasevi, 1996). If one followed the CIOMS guidelines, and if one identified Thailand as an ‘underdeveloped’ community in relation to the sponsoring country, the US, this would not be permissible. However, if what seems more reasonable, one identified certain conditions that should be fulfilled before one carried out a trial in one country that is not carried out in another, such as whether the outcome would benefit the host country and whether there is a satisfactory research review procedure in place, one would not necessarily conclude that this phase I/II vaccine trial of a vaccine against subtype E is unjustified even though the trial is not carried out in the US. This is also reflected in the recent revision of the Thai National Plan on AIDS Vaccine Development" (1997), which now states that one can carry out two types of phase I/II trials in Thailand:

> A. Repeat Phase I, Phase II or I/II trials of selected candidate vaccines initially tested in the country of origin of the vaccine. These studies are important to confirm their safety and immunogenicity profile before proceeding to Phase III (efficacy) trails of these candidate vaccines in Thailand.
>
> B. Initial Phase I trials of selected candidate vaccines which may be specifically appropriate for Thailand, because of their antigenic composition (such as HIV-1 subtype)

> or vaccine design. Specific criteria for admission of candidate vaccines for Phase I/II clinical trials will be developed and continuously revised by the "Technical Subcommittee on HIV/AIDS Vaccines."

This revision is in agreement with the position taken in this paper on phase I trials.

In addition to the need to do phase I/II trials in order to test vaccines against subtypes prevalent in one's own country, there may also be a need to carry out these trials for other reasons. This point is made by Dirceu B. Greco: "In many situations a repeat phase I trial will be very useful: to check for variations in genetic and immunological response; if it is confirmed the need for tailored vaccine epitopes (related to the clade or clades disseminated in a country); it facilitates the discussion of the protocol between investigators from the host and from the country of origin; it will better prepare (or check) the available infrastructure" (Greco, 1997). The same points are made by Peter Wright "there are a number of different settings in which replicate experiments are validly done to evaluate comparable or identical vaccines or to determine the value in a particular country of an approach to immunization. Many examples exist with current vaccines of different performance in a developing country setting ... safety and more frequently immunogencitiy parameters will differ in developing countries that may alter the risk benefit ratio. The logistics of an AIDS vaccine efficacy trial are almost overwhelming and must be addressed in a step wise fashion in smaller trials. One must determine with a smaller trial whether recruitment, education, retetion, data management, and laboratory analysis can be performed at the site"(Wright, 1997).

One final point also underscores the need to do separate trials in developing countries. As Peter Wright has pointed out that "it must be clear that although one or two trials can be done in the US, and perhaps one trial in Europe, the answer for an AIDS vaccine is going to come from the developing countries, and to decide that it is unethical to do trials in this setting is to declare that HIV will be a continuing unresolved global problem"(Wright, 1997).

3.DIFFERENT ECONOMIC CONDITIONS IN DIFFERENT COUNTRIES

Finally, we come to what is probably the most difficult case. How should one deal with the fact that there are different economic conditions in different countries, making some treatments unavailable in many countries? Specifically, is one always obligated, as the Helsinki declaration seems to imply, to provide the best proven therapy to participants in research subjects? This topic will be discussed by examining the recent controversy over perinatal transmission studies where this is precisely the issue.

The perinatal transmission studies

In 1994 the ACTG protocol 076 showed that treatment with AZT five times a day for an average of 11 weeks before giving birth, intravenous treatment during labor, as well as treatment of the child for 6 weeks after birth, resulted in a reduction in HIV-transmission from 25% to 8%. The

treatment regimen costs at least $800. It is recognized that it is not possible to introduce this treatment in developing countries, both because of its cost and for logistical reasons. Because of this, a number of clinical trials have started or are planned with shorter course of AZT treatment. Most of these trials are carried out in developing countries.

The CDC has justified the trials in a document publicly available on the WEB. It is worth quoting at length from this document:

> The CDC is not using the ACTG-076 regimen in the current studies because although those results have changed the standard of care in the United States and other industrialized countries, the standard of care for treating HIV infected pregnancies in most developing countries remains "no intervention." The intent in the current studies is to answer the question which is most relevant for public health decision makers in developing countries: "Does AZT, when given at this specific dose for four weeks, result in a lower perinatal HIV transmission rate compared to untreated women. There is consensus at WHO, UNAIDS, and in countries where these trials are being conducted that the full regimen of ACTG-076 could not currently be implemented as standard of care. Another reason that placebo trials have been recommended is because it is necessary to change multiple parameters from the ACTG-076 regimen ... A placebo trial is the most scientifically valid way to determine the effect of these changes. Moreover, a placebo design ... allows for a "streamlined study" which can provide an answer within one to two years after the start of the study. ... A study design that compares a short AZT regimen with the long ACTG-076 AZT regiment would not meet the study objectives, in other words, it would not answer the question, "Does short course AZT work to prevent perinatal transmission?" This would not indicate whether the short AZT regimen was better than the currently available intervention -- nothing at all. ...One of the most important ethical considerations in conducting clinical trial research is that participants in the research should not receive less care than would be available to them if they were not involved in the research. Since AZT is not currently available for perinatal HIV prevention in Thailand and Ivory Coast, the placebo-controlled trial design is consistent with that principle.

Not everyone shared this opinion, however. Already in 1995, the investigators responsible for the non-placebo controlled trial wrote in a letter to *Science*:

> We firmly believe that it would be unethical to incorporate a placebo arm in our study in Thailand. ... Adding a placebo arm to our study design could provide added reassurance that the 076 regimen is as effective in the Thai population as in the original study and a more definite estimate of the degree of efficacy of the shortened regimen over no treatment. However, we believe that this scientific justification does not outweigh the ethical imperative to provide all subjects with a treatment that is consistent with current scientific knowledge about the efficacy of AZT in preventing transmission and with the emerging standard of care in the country in which the study is undertaken (Lallemant et al., 1995).

Although the criticism of the placebo studies was voiced in the literature from 1995 (see for example (Cohen, 1995)), not much happened until the Public Citizens's Health Research Group criticized the trials in a congressional hearing on bioethics May 8, 1997 (Cohen, 1997). The story was picked up by a variety of news agencies in the countries concerned. The placebo trials were criticized by for example Robert Kuttner in the Singapore Straits Times (Kuttner, 1997), in Uganda and in Thailand (Bhatiasevi, 1997). The placebo trials were compared with the Tuskegee syphilis studies, and it was argued that more than 1000 children in developing countries would die unnecessarily. The hearing was also picked up by press reports in North Carolina (Ready, 1997) where the NGO Family Health International involved in the study and Glaxo Wellcome both are located. The NGO was clearly troubled by the criticism. In this press report it was also apparent that at least the bioethicists interviewed at that time to a large degree were sympathetic to the claims by Public Citizens Health Research Group, although finding it difficult to draw a firm conclusions. It was also clear (Cohen, 1997) that a number of officials from the developing countries themselves supported the trials. Jon Cohen, for example, writes that "Edward Mbidde, chair of Uganda's AIDS Research Committee ... wrote that he read Public Citizen's arguments with 'dismay and disbelief'. He described their attacks as 'patronizing' and said it reeked of 'ethical imperialism'." He also reiterated the argument that a placebo trial is necessary to find out whether a short course is better than nothing; The alternative trial without placebo might conclude that an shorter treatment is inferior, although it in fact might be better than placebo.

The criticism by Angell, Lurie and Wolf

These stories went largely unnoticed by the general media until Marcia Angell criticized the trials in an Editorial in the New England Journal of Medicine, September 18, 1997 (Angell, 1997b). The editorial was accompanied by a Sounding Board article by Lurie and Wolfe from the Public Citizens Health Research Group (Lurie & Wolfe, 1997) . They argued that the placebo-controlled trials are unethical as they deny the control group a proven beneficial treatment. According to the Helsinki-declaration, all the participants “should be assured of the best proven diagnostic and therapeutic method”. They also show that a placebo trial would not require fewer subjects nor would it take longer to get the necessary results. In their article, Lurie and Wolf countered the arguments that, as no treatment is the standard of care in developing countries research subjects in the placebo group would not be denied the available treatments in that country, by pointing out that the reason for this standard of care is economic. However, it would not be difficult for economic reasons to provide the participants in the study with AZT in the required amount: this would not add much to the cost of the study. They recognize that it may not be justifiable to provide more expensive forms of care, such as treatment in coronary care units.

The New England Journal of Medicine Editorial was picked up by newspapers such as the New York Times (Stolberg, 1997). In a subsequent Op-Ed letter Joseph Saba of UNAIDS and Arthur Amman of the American Foundation for AIDS research defended the trials. (Saba & Amman, 1997). They argued that the trials conformed to international guidelines, had been approved by ethics committees in the countries concerned, and were necessary in order to find an

effective intervention for a great health problems. Critics would be guilty of "imposing their standards of care on developing countries. Local health experts, bioethicists and affected groups are best qualified to judge the risks and benefits of any medical research", and the trials "adhere to one of the basic ethical principles of any study, regardless of locale: that the planned intervention can be applied in the country in which it is tested". In a reply, Marcia Angell pointed out that the trials did not conform to the Helsinki declaration and cited the passage quoted above; it was therefore not a matter of imposing US standards on others, but breaking an international agreement. She also maintained that "researchers knowingly consign many newborns to H.I.V." (Angell, 1997a). A member of the New England Journal of Medicine editorial board, David Ho, criticized the editorial by Marcia Angell, and he subsequently resigned from the Editorial Board in protest against the editorial (Ho, 1997). The editorial was defended in a subsequent editorial authored by both the Editor in chief and Marcia Angell (Kassirer & Angell, 1997).

Varmus and Satcher clarified the position of the CDC and NIH in a subsequent article (Varmus & Satcher, 1997). In this article they argued that "the most compelling reason to use a placebo-controlled study is that it provides definite answers to questions about safety and value of an intervention in the setting in which the study is performed, and these answers are the point of research ... comparing an intervention of unknown benefit - especially one that is affordable in a developing country - with the only intervention with a known benefit (the 076 regimen) may provide information that is not useful to patients. If the affordable intervention is less effective than the 076 regimen - not an unlikely outcome - this information will be of little use in a country where the more effective regimen is unavailable. Equally important, it will still be unclear whether the affordable intervention is better than nothing and worth the investment of scarce resources" (p. 1004-1005).

Arguments for and against the trials with placebo controls

From the above, we can identify the following arguments in favor of carrying out trials with placebos in developing countries:

- The benefit to future millions of babies exposed to HIV outweighs the possible risks to the few babies in the placebo controlled clinical trials
- The participants in the clinical trials get standard of care in their own countries. They are not denied treatment they would otherwise get
- The trials have been approved by local ethics committees and local community representatives. Refusing to carry out these trials would be an imposition of external values
- These trials differ from the Tuskegee trial in that the women have given their informed consent to participate
- The placebo trials are the only way to get results that are truly useful for the countries themselves. As such they conform to the principle that research should be responsive to the health needs of the country.

The following are the main arguments against carrying out the placebo trials:

- The trials violate international guidelines
- The trials knowingly expose children to risk of HIV infection that could be avoided

Let us examine these arguments.

First, I think it should be recognized that the placebo controlled trials clearly violate both the Helsinki declaration and the CIOMS guidelines, in spite of the fact that several defenders of the trials have maintained that they are in accord with established international research ethics guidelines. The CIOMS guideline 8 clearly prohibits phase III trials in a host country that is not simultaneously carried out in the sponsoring country, and the Helsinki declaration demands that participants in trials receive the best proven therapy. It is remarkable that officials in the involved agencies, such as UNAIDS, CDC and NIH, do not seem to have been aware of the contents of these guidelines until the controversy over these trials arose. Much of the subsequent controversy could probably have been avoided if the controversial issues had been faced head on in 1994-95 when these trials were in the planning stage.

Second, it should also be recognized that one cannot simply reject the trial because it does not conform to international guidelines. Although the fact that a proposed trial is not in accordance with international guidelines is something that should be taken seriously, one has to take into account that the guidelines may be inadequate or that the guidelines may have to be modified in light of new information. One needs to provide an argument that it is correct to follow the guidelines as well as to provide arguments for why it is justifiable to violate the guidelines. Having said that, however, one should also recognize that only in unusual circumstances should one violate international agreed standards for the conduct of clinical trials. Examples such as the perinatal transmission studies may show that the guidelines need revision. Ideally, though, this revision should take place before the trials in question are initiated.

Third, I think it should also be recognized that simply justifying the trials by referring to the fact that HIV transmission to newborns represents a major health problem in developing countries is not acceptable. Ever since the Nürnberg process it is a firmly accepted principle of research ethics that research on humans need to satisfy additional conditions, and that there are times when we justifiably conclude that research should not be carried out, even though the results of the research might be of great benefit to future patients. This is reflected in the principle of the Helsinki declaration that “concern for the interests of the subjects must always prevail over the interests of science and society”, although this may be a too strong formulation of the underlying principle (see below).

Fourth, one should also reject the argument that the trials are acceptable because the participants have knowingly consented to the trials, and that this fact makes these trials different from the Tuskegee experiment.The issue is what trials should be approved in a particular country, before the choice is presented to potential participants for their acceptance or rejection. There is of course the question of what input affected communities should have in that decision, and they may want to approve a trial as a way of getting access to a new promising therapy, but that is

separate from the consent that an individual gives to participate in a trial. Furthermore, accounts from the field sites indicate that there are severe deficiencies in the informed consent process and it is questionable whether participants in these trials have a sufficient understanding of what they have consented to. In Uganda, for example a women with a degree in law said "that she had never been made to understand that he medicine being tested, AZT, was already known to stop transmission of the virus during pregnancy. 'I am not sure that I understand all of this so well, Nicole said, but there were some medicines that they said might protect the child, and they wanted to follow the evolution of my pregnancy and the effectiveness of treatment.' ... Then asked what how she would feel if she learned tomorrow that she had received a placebo when a proven treatment existed, Nicole's tone changed abruptly. I would say quite simply that is an injustice, she said" (French, 1997). In my opinion it is necessary to justify trials in a two stage process. The trial is first reviewed by an appropriate ethics committee. A trial which is rejected at this stage, should not be carried out. In addition, participants need to give their individual consent to participate in the trials. This paper is mainly concerned with the first stage of this process, not with the informed consent procedures.

Having said that, let us now reconstruct the main argument *in favor* of placebo controlled trials. It depends crucially on the judgement that carrying out a placebo controlled trial is the only way to gain useful knowledge, on the claim that people taking part in the trial are not made worse off then they would be if they did not take part in the trial, and on the judgment that on balance, the good consequences of doing the trial far outweigh the bad consequences of doing nothing. Although the argument in that sense is a consequentialist one, it is not incompatible with maintaining that some actions are wrong independent of their consequences. As will be seen below, the argument is not necessarily incompatible with the fundamental tenet of modern research ethics that one cannot inflict harm on research participants for the sake of benefit to future patients.

The argument, then, is the following: Everybody agrees that perinatal transmission of HIV is a great problem, and that an effective, affordable and suitable therapy for developing countries is urgently needed. The only way to find out if a short course AZT treatment is effective is to do a placebo controlled trial. This would involve giving some participants in the trial a known ineffective treatment, thus exposing them to danger. This could be construed as a case of knowingly exposing participants in the trial to a risk for the sake of benefit to future patients or for the sake of benefit to society. If that were the case, it would violate one of the fundamental principles of research ethics. The fact is, however, that right now some people do not receive the care and treatments they need, and this will continue for quite some time into the future. This may be unjust all things considered, but there is little, if anything, we can do to change that in the foreseeable future. Specifically, if a trial is not carried out, newborns will be exposed to HIV without treatment in many developing countries. There is, given the way things are, nothing one can do that would change this fact either, at least in the foreseeable future. The alternative would be to give some women a therapy that might be effective against HIV transmission, at the same time as one can find out whether this short course therapy is really effective, and thus would offer a hope to avoid HIV transmission in the future. No treatment that ordinarily would be offered are withheld from the women taking part in the trial, thus fulfilling CIOMS guideline 15 which states that :

> Sponsors and investigators should refer for health care services subjects or prospective subjects who are found to have diseases unrelated to the research, and should advise prospective subjects who are rejected as research subjects because they do not meet health criteria for admission to the investigation to seek medical care. *Sponsors are expected to ensure that research subjects and the communities from which they are recruited are not made worse as a result of the research* (My emphasis).

The alternatives one has to choose between are therefore:

> 1) Do nothing. All women in the country of the proposed trial who are now HIV positive would receive no treatment to prevent transmission, as well as all HIV positive women in the foreseeable future;
>
> 2) Do a clinical trial. This would mean that some women would receive a treatment that might be effective in reducing the chance of transmission, as well as the possibility of establishing that this treatment is effective, and thus prevent transmission in a substantial number of future cases.

In such a case, the only responsible thing to do would be to carry out a placebo controlled clinical trial.

One problem with this argument is that it is similar to arguments presented in favor of the the Tuskegee and the Willowbrook studies, and which have been rejected by most commentators. The researchers involved in both of these trials defended them arguing that the participants were no worse off in the trial then they would be if they did not take part in the trial. According to David Rothman:

> The Tuskegee study, the USPHS [U.S. Public Health Service] insisted, constituted a 'natural experiment'" ... Macon County, USPHS maintained, was a 'ready made laboratory.' Even if the USPHS were to forego the opportunity to track syphilis of the Macon County blacks, it seemed certain that this poverty-stricken, isolated, and medically unserved population would never receive the only therapy that existed - a complicated, lengthy and somewhat dangerous, and not altogether effective treatment of mercury and the two arsenic compounds known as salvarsan. ... The project was ethical, the researchers could claim, because they would only be watching the inevitable. Since the subjects were not going to obtain treatment anyway, there was no reason to miss the opportunity to trace the effects of their infections (Rothman, 1982).

Similarly for the Willowbrook study. In this project in an orphanage the researchers gave the newly admitted children hepatitis infection using the argument that it was highly likely that they would be infected anyway because of the hygienic conditions of the place, and that it was better for them to be infected under controlled conditions. According to Rothman:

> What harm or ethical violation would occur by administering the virus oneself, observing

the course of the disease, and, in this instance (but not in the Tuskegee one) attempting to find a cure?

Rothman argues against the position taken by the researchers involved in these two studies. According to him, "there is an essential difference between taking advantage of *social*, as opposed to biological, conditions. ... Predictions of continued social deprivation .... tend to become self-fulfilling. ... Experiments that build upon social deprivation are likely to manipulate the consent of the subjects". And finally, according to Rothman, once researchers start such a research project they no longer are mere observers of the phenomena, but become "accomplices to the problem". When they start to recruit research subjects, one could argue that they have special obligations towards them, obligations that they do not have towards disadvantaged social groups in general.

If we generalize from Rothman's examination of these two cases, the main argument *against* the placebo trials is the following. It depends crucially on the acceptance of a principle that it is always wrong to do an action of a particular type, irrespective of the consequences: Giving a placebo to some of the women is a deliberate act of withholding a known effective treatment to identifiable individuals when one could easily provide that treatment. It would not for example represent an extraordinary expense to provide that treatment to the participants in the trial, and would not add much to the budget of the trial as a whole. The argument that the women would receive no treatment if they were not part of the trial is not valid. There is a general obligation to provide effective, and in this case, life-saving treatment to people if they need it. One may nevertheless recognize that this ideal is not always fulfilled. In the US, for example, some people do not have insurance, and consequently do not always receive needed treatment, but this is recognized to be a flaw in the system. Similarly, because of economic conditions, many people in developing countries do not receive needed medical care. We *are* under an obligation to do what we can do rectify that situation, although we must also recognize that it is not always possible to do much about it. It is therefore quite another thing altogether to deliberately design a trial where some women would get an inferior treatment when we could easily do otherwise. An additional argument against the placebo trial would be that we have special obligations to participants in trials. Participants in clinical trials typically take some risk by agreeing to be randomized to one treatment of unknown benefit. In such a context we at least have the obligation to ensure that we do not knowingly expose them to an identifiable danger.

This argument presupposes that there are some actions that are wrong even though the consequences of doing these actions may be better than refraining from doing them. As is usual in arguments of this type, proponents of the argument need not argue that the action is right or wrong *whatever the consequences*. In the argument outlined above, for example, it is stated that it is wrong to knowingly withhold an effective treatment when one could easily provide it, pointing out that providing AZT in the trial would not add much expense to the trial. Given other types of consequences, one may reach a different conclusion. If, for example, one wanted to do a clinical trial in a developing country on the effects of aspirin on survival after myocardial infarction, offering bypass surgery to trial participants may not be regarded as a treatment one could easily provide, given the need to build coronary care units and train and pay highly qualified staff. Offering state of the art antiretroviral therapy to trial participants may fall somewhere in between, costing $12-15.000 per year and once initiated would have to be provided for the rest of the

patient's life (see Bloom, 1998, and the discussion below on the South African case).

These, then, are the arguments on both sides of this controversy. As we have seen above, a fundamental presupposition among those who favor the placebo controlled trials is that a placebo controlled trial is the only way to obtain useful knowledge for developing countries. The counter-claim is that a trial without placebo would produce just as useful results, and in the debate it has been assumed that a study with the 076 regimen as the control group would be ethically justifiable. As this issue is so crucial it is necessary to examine it separately, if we are to make any progress in resolving this controversy.

Can useful results be obtained with a non-placebo controlled trial?

Lurie and Wolf claim in their article that it would be possible to obtain useful results by carrying out an equivalence trial comparing the current treatment against the treatment with a reduced dosage (for a discussion of equivalence trials, see Ware & Antman, 1997). In order to do that one would use as the null hypothesis the claim that the standard treatment reduces perinatal transmission by at least a specified percentage over the experimental treatment. The claim could for example be that the standard treatment reduces perinatal transmission by more than 5 percentage points compared with the experimental treatment. If this null hypothesis is true, then the two treatments are not equivalent, if it is false then the two treatments are equivalent. Based on this, on can calculate the necessary sample size associated with desired error probabilities. Lurie and Wolf claim that it is possible to carry out such a trial using the same number of participants as a placebo controlled trial. This claim is not in dispute.

If the trial results in a rejection of the null hypothesis, i.e. an acceptance of the two treatments as equivalent, we can conclude that the two treatments do not differ by more than 5 percentage points. If the trial results in an acceptance of the null hypothesis, we can conclude that there is at least a 5 percentage point difference between the two treatments. It is at this point that the arguments made by people such as Mbidde, Satcher and Varmus become important. According to them, if we accept that the two treatments are not equivalent in this sense, the experimental treatment may still be useful to developing countries. If we assume that the perinatal transmission rate is 25% without any treatment, the experimental treatment may result in a transmission rate of 10%, representing a significant reduction in transmission that would still be of interest to developing countries.

One obvious answer to this worry would be to redefine the null hypothesis as a difference by more than 10 percentage points, or whatever transmission rate would be of value to a developing country. The problem with this strategy is that in order to determine the transmission rate that would be of value for the experimental treatment, one would have to give an estimate for the transmission rate without treatment. But the estimate could be wrong by a number of percentage points for the population under study, and this cannot be known if a placebo controlled trial is not carried out, thus supporting the arguments of Mbidde, Satcher and Varmus.

The controversy over whether a non-placebo controlled study can yield useful results thus boils down to a controversy over whether one judges it to be likely that the experimental treatment will reduce perinatal transmission close to what was found in the ACTG 076 regimen,

and whether one can make reliable judgements about the perinatal transmission rate if no treatment is given. Clearly this is a point where reasonable people can disagree.

Those who have criticized the placebo controlled studies have advocated trials where the ACTG 076 regimen is used for the control group. The problem with this suggestion is that this trial design is subject to the same counter-arguments as the placebo controlled trials. Usually, when a trial is initiated it is because the currently available treatment is unsatisfactory in one way or another. It may be that it is not particularly effective, and a new experimental treatment may be more effective. Or it may be that the currently available treatment has unacceptable side-effects, and a new experimental treatment may have fewer side-effects, although it may not necessarily be more effective. Or, of course, it may be a combination of both. According to the commonly accepted position, in such a situation of genuine uncertainty as to which treatment is better for the patient, it would not be unethical to randomize the patient group to standard treatment and experimental treatment. A completely different situation would arise, however, if the currently available treatment is unacceptable *because it is too expensive*. If there is no reason to expect that the new treatment is better, or has fewer side-effects, than the currently available treatment, and that the most that one could hope for is that it is equivalent in terms of efficacy and side-effects, how can one then justify the trial in terms of clinical equipoise? This would seem to be exactly the case with regard to the protocol using the 076 regimen as control. The main argument against the placebo trials was that one knowingly exposed identifiable women to a known to be inferior (placebo), or put another way, one withholds a known superior treatment from one group of the women (the 076 regimen). In the alternative case one does exactly the same things. One withholds a known effective treatment from one group of women, providing a treatment that is cheaper, but with no reason to expect any benefit to the participants in the trial over and beyond the benefit provided by the known effective treatment. Of course, it might be the case that some women would prefer a shorter regimen because of the possibility that this would give them a lower chance of developing AZT resistant strains. That is, there may be some women who would be indifferent between the shorter course vs. the longer course of treatment. But if that is the case, the trial could have been carried out in the US, and the trial would violate the principle that it should be carried out simultaneously in both sponsoring and host country. This trial might provide useful results for the sponsoring country, may not provide useful results for the host country, yet is only carried out in the host country. Thus the non-placebo trial is subject to the same counter-arguments as the placebo trial and in addition is liable to the charge that it exploits developing countries, in contrast with the placebo controlled study the results from which will only be of use for the host country. Contrary to the claims made by Lurie and Wolf it would seem that their suggested alternative is subject to even stronger ethical counter-arguments.

The conclusion from this discussion is that one may reasonably conclude that carrying out a placebo controlled trial is the only way to obtain knowledge about a treatment that can be useful for developing countries. Although, as has been shown above, one may also disagree with this judgement, and it is this disagreement that is some of the basis for the controversy over the acceptability of the placebo-controlled perinatal transmission studies. In fact, it would seem that even in Thailand AZT is not yet generally available to HIV positive pregnant mothers. According to a news report on March 27, 1997 (Emerging Markets Datafile Nation, 1997) Dr. Virat Sirisanthana of Chiang Mai University argued that because of price reductions AZT should now

be offered to all infected pregnant women. However, senior medical officers of the Ministry of Health, Dr. Viwat Rojanapitayakom and Dr. Vichai Chokeviwat, pointed out problems such as testing one million pregnant mothers a year, and concluded that they would wait the results of ongoing studies before making AZT available. This observation would tend to support the official CDC and NIH position against the position of the Harvard group proposing a non-placebo controlled trial in Thailand.

Concluding discussion of the perinatal transmission studies

I think it is fair to conclude from the discussion above that there is room for legitimate disagreement about the ethical justification of the placebo trials. It is difficult to defend the position that these trials are obviously unethical. It is, however, also difficult to defend the position that these trials are ethically unproblematic. The controversy over these trials is based partly on disagreements about fundamental ethical theories, such as the acceptability of a general consequentialist approach versus an approach that takes it to be morally wrong to perform certain actions, such as directly causing preventible harm to an identifiable individual. The controversy is also based on disagreements about general issues in clinical trial design, both methodological and ethical. It is therefore an area where reasonable people may reach different conclusions.

I also believe, however, that a stronger conclusion can be drawn from the examination of this controversy. If it is the case, as I have tried to show above, that both the placebo and the non-placebo trials are subject to the ethical worry that one knowingly exposes one group of women to a treatment believed to be inferior for the sake of gaining knowledge which will be useful for the treatment of future patients, it does suggest that some of the principles in the current research ethics guidelines need to be revised. If one followed the strict interpretation of the Helsinki-declaration forbidding any risk to the research subjects justified solely in terms of societal benefit, or forbidding providing treatments known to be inferior, research that would be immensely valuable for developing countries cannot be carried out. That is, there are cases where reference to different economic conditions in different countries may be ethically justifiable. Specifically, if as is the case in the perinatal transmission studies, the following conditions are fulfilled, it would seem justifiable to carry out a trial in developing countries that is not carried out in the sponsoring country:

- The trial is the only way to gain useful knowledge for the host country
- The results of the trial will primarily benefit the host country and not the sponsoring country
- The research subjects are not denied care or treatment they would ordinarily get in the country where the trial is carried out

Let us briefly examine these conditions, noting the differences between the perinatal transmission studies and the Willowbrook and Tuskegee studies. If Rothman's arguments are correct, all three studies satisfy the third condition. If this were the only justification for carrying out the perinatal transmission studies, they would be subject to the same counter-arguments as the Willowbrook

and Tuskegee studies. The perinatal transmission study, however, differs in one fundamental aspect. If this study is not carried out in the countries involved, an effective and affordable treatment will simply not be available for these countries in the foreseeable future. This is reflected in the first two conditions which, taken together with the third condition, in my mind constitute a powerful argument in favor of conducting these trials. The Tuskegee and the Willowbrook studies were not primarily carried out for the benefit of the social groups involved in these studies, and it is also uncertain whether they were the only way to obtain useful knowledge. It should also be clear from my discussion that I believe the placebo controlled perinatal transmission studies satisfy all three conditions, whereas the non-placebo controlled trials may violate the first two conditions.

The debate in South Africa about whether a pharmaceutical company is obligated to provide treatment after the trial

In a recent issue of the British Medical Journal there was a debate about whether pharmaceutical companies are obligated to provide therapy after a clinical trial has ended. According to (Cleaton-Jones, 1997) pharmaceutical companies are submitting application for protocols for trials with various combinations of drugs to treat HIV disease in countries such as South Africa. He presents the following dilemma: "What is the responsibility of a trial sponsor to a trial subject who responds to treatment that will not be available after the end of the trial ... If a patient infected with HIV responds to the test drugs, may one ethically withhold the drugs at the end of the trial, thereby depriving the person of benefit?" Although it has been a practice to provide such treatment after a trial before, the advent of combination therapy has raised new problems, as a pharmaceutical company may have to purchase and provide the products of competitors. Cleaton-Jones' own position, and that of the ethics committee he belongs to, has been that this is not justified. Critics of that position have pointed to two arguments against it. First, the trial participants have knowingly given consent to participate in a trial on the condition that they will not receive the drugs after the trial has ended. Second, since many patients in South Africa do not receive any treatment at all, taking part in a trial, even under the condition that the drug will not be continued after the trial has ended, will be better than nothing. The executive direct or NAPWA (the National Association of People Living with HIV/AIDS) gives some support to these arguments against the policy of the ethics committee, although he points out that the opinions in the community of HIV infected people are divided on the issue (Busse, 1997). Other commentators supported the position of the ethics committee ((Emery & Cooper, 1997; McLean, 1997)). The accompanying editorial also seems to give support to the position of the ethics committee (Wilmshurst, 1997).

What makes this case special is the fact that response to medications against HIV disease varies from person to person. Some people may respond to one medication, but not another. If it has been found in the course of a trial that a person does respond to a particular medication, it would seem that this gives one a special obligation to continue to provide this treatment to that person, even after the trial has ended, and even though this medicine is not generally available to others for economic reasons. This case illustrates is that some believe that we have special obligations to participants in research, a point also emphasized by Margaret Somerville arguing

that a *fiduciary relationship* may exist between researchers and participants "governed by more stringed ethical and legal requirments than, for example, a contractual relationship" (Somerville, 1997). This argument would again depend on a general view that people who participate in trials take some risks by participating in the trial for the sake of future patients and are therefore entitled to some benefits. We have seen above that not all people accept this argument, instead focusing on the possible benefits participation in a trial may have for the people concerned. The disagreement over whether one is obligated to continue treatment would seem to depend on one's general views with regard to the ethics of clinical trials.

4. PREVENTIVE HIV VACCINE TRIALS WITH SECONDARY ENDPOINTS

Let us now use all of the arguments developed above to examine the case of preventive HIV vaccine trials with secondary endpoints. The question is whether one can carry out such trials in developing countries, but not in developed countries, because treatments which reduce viral load are not available in developing countries. The conclusion from the discussion above is that there are cases where it is justifiable to take into account different economic conditions, and the question is whether this is one such case. One should also note, however, that there is a general ethical issue here for all vaccine trials, not just vaccine trials with secondary endpoints. As Peter Wright has pointed out the questions are whether "you treat with US antiretroviral and opportunistic infection prophylaxis protocols all seropositives enrolled in screening, do you treat seropositive partners in sexual transmission trial, do you treat infections occurring during the trials in vaccines or placebo. Or is there an option of delivering the best available care in the community or country for what remains palliative therapy for a universally fatal disease"(Wright, 1997). If as some seem to maintain, vaccine trials will most likely be carried out among uninfected partners of HIV infected individuals, then it is necessary to address the question about what type of interventions one should offer the individuals taking part in the trials, both before the trial starts (counseling) and during the trial should they become infected (antiretroviral therapy) (Bloom, 1998). The first thing that needs to be done is to specify why the treatments are not available.

First, they may not be available because reasonable physicians differ about whether such treatments should be regarded as standard of care independent of economic considerations. For example, right now, there is disagreement about whether one should initiate aggressive treatments with the aim of reducing viral load immediately after a person has become infected. If the reason for non-availability is a reasonable disagreement among experts, then one can, as shown above, justify initiation of studies in a host country that is not carried out in a sponsoring country. This is underscored by Dirceu B. Greco who says that at least now "if we consider that the set point (stabilization of viral load) will occur around 6-12 months after infection there is plenty of time to get samples to determine these data before a proper referral is made (Greco, 1997)." Barry Bloom, however, makes the point that "withholding of drug treatment until viral loads can be determined at more than a single time point would constitute another major ethical problem" (Bloom, 1998).

Second, the treatments may not be available for economic reasons. Under this scenario it

is assumed that experts agree on a standard of care, but this standard of care is too expensive for a developing country. I have above examined the general arguments for and against doing a trial in a developing country in such a case. Simply referring to a difference in risk vs. benefits is problematic. The discussion about the perinatal transmission trials showed that the acceptability of doing a trial depends on the following conditions:

- The trial is the only way to gain useful knowledge for the host country
- The results of the trial will primarily benefit the host country and not the sponsoring country
- The research subjects are not denied care or treatment they would ordinarily get in the country where the trial is carried out

One should recognize, however, that a decision to go ahead even if these conditions are fulfilled will be controversial as some people will believe that it is always wrong to expose people to danger that could easily be averted, as shown in the discussion about the perinatal transmission trial. This is an issue where reasonable people can differ and it would therefore be wrong to conclude that carrying out trials under these conditions would always be unacceptable.

Third, the ethical dilemma in this case also has another dimension that one might utilize in order to justify these trials, but which also creates special problems. The treatments provided are not necessarily part of the research protocol. One might therefore suggest that one's obligation to the research subjects is only limited to providing whatever is in the protocol. What is done for them outside of that setting is the responsibility of others. Specifically, if people become HIV infected during the study, they would be cared for in the same the way as all others who become HIV infected in that particular country. If usual care in that country is no treatment, then that is what they would get. If usual care is a particular treatment, they would get that. It is this fact that makes it possible to do the trial in one country but not in another. This fact is, however, unrelated to the protocol of the trial, and therefore cannot be used as a basis for judging that the trial is ethically acceptable or not. This argument depends on whether one can make a defensible distinction between what is provided as part of the research and what is provided outside of the research setting. The idea is that even if one in general can not defend doing trials in developing countries, the vaccine trial with secondary endpoints have certain features that nevertheless make it possible to justify doing these trials in developing countries but not in developed countries. There are, however, in my mind several problems with an attempt to argue that one can make a *general* distinction between what is done for research purposes and what is done as part of treatment outside the research protocol.

First, the argument assumes that becoming HIV infected is unrelated to the trial. There is a possibility that participants in trials will increase their risk behavior as a result of taking part in the trial, because they believe that they are protected. Taking part in the trial may therefore have some causal relevance to becoming infected. If that is the case, it is the responsibility of the researchers to provide treatment for what can be regarded as a trial related injury. There is also the possibility that the vaccine actually makes the disease progression worse once the person becomes infected. This also places an obligation on the researcher for what can be regarded as a trial related injury.

Second, a general policy of not providing treatment to patients who become HIV infected, because that is in the interest of the research being undertaken, places an unacceptable conflict of interest on the researchers. Presumably, some people would be able to obtain treatment, even though the treatment may not be generally available in the country. The researchers would have a strong motivation to discourage people from seeking treatment if it is part of the protocol that people who become HIV infected should not obtain treatment.

Third, the fact that people will obtain treatment, even unrelated to the research question, has been seen as a motivating factor for people to take part in clinical trials, and has even been encouraged even in the setting of HIV vaccine trials. It has for example been suggested that one should offer hepatitis B vaccine to participants in HIV vaccine studies. Because of the perceived health benefits of such a vaccine, more people might be motivated to take part in the trial. Other suggestions include offering health care vouchers to trial participants (Beyrer et al., 1996). It would create an impossible double standard if a treatment is specifically excluded in cases where that is not in the interests of science. On the other hand, it is important to note that providing treatment to participants in a trial that would not ordinarily provided to other people in the country, can be regarded as undue inducement to participate, thus violating research ethics guidelines, as argued by Wright and Somerville (Somerville, 1997; Wright, 1997). Before one makes a distinction between research and treatment one would have to provide general criteria for when providing treatment in the course of research is acceptable and when it is not.

Fourth, the South African case has shown that one might have special obligations to people taking part in research. With regard to vaccine trials one could make a stronger case for this position compared to clinical trials where one compares treatments. Vaccine trials represent a more uncertain benefit for the people in the trials than trials of treatments for disease.

All of these are arguments against a general distinction between what is done for research and what is done as part of treatment outside a trial. This does not mean that in specific cases it may be justifiable to make this distinction, but I do think that it would be preferable to justify these trials in terms of the general three conditions identified above, rather than to attempt to introduce a distinction between treatment that is provided as part of the research protocol and treatment that is the responsibility of others.

5. THE ROLE OF RESEARCH ETHICS GUIDELINES AND RESEARCH ETHICS REVIEW PROCEDURES

The discussion above should have made clear that the ethical issues related to international collaboration are quite complex and controversial. Because of the real possibility for abuse and exploitation, international guidelines for the conduct of such trials are necessary and desirable. However, I believe I have shown that the current guidelines are in need of revision on a number of points. This raises the general issue of how one should act in relation to a specific clinical trial which does not conform to the current guidelines, but where a case can be made that the trial nevertheless is ethically justifiable. One could argue that the researchers and the research ethics

committees involved should be able to make the case for the trial's acceptability even though it violates international guidelines. I do believe that there are good reasons for not accepting this strategy as a general policy. These reasons were pointed out to me by Robert Levine in a comment to an earlier version of this paper. Researchers have an obvious interest in promoting their research and would not be the best group to argue why guidelines should be violated in a particular case. Research ethics committees reviewing the particular trial are usually bound in their mandate to follow the guidelines. In general, when a controversial case arises, one should attempt to develop a broad consensus that is then reflected in a change in the guidelines, before a specific trial is initiated. There may, of course, be cases where it is not possible to follow this general policy, but these should be the exceptional cases, and would require special justification.

The current guidelines use quite specific rules, such as requiring that phase III trials be carried out simultaneously in two collaborating countries. There are of course good reasons for wanting to defend a principle that says that research subjects should always receive the best proven therapy, or a principle that says that phase III trials should always be carried out simultaneously in two countries. Adhering to such very specific principles would undoubtedly prevent abuses, and it may be desirable to have simple and unequivocal rules for the conduct of trials. It is, however, also likely that adhering to such principles would prevent one from carrying out trials most people would find acceptable. These types of decisions are always very complex, and one must always examine each case in light of broader principles, and accept that certain decisions will not be unanimously accepted but that it nevertheless may be necessary to decide one way or another. If that approach is taken, it means that the countries where the trials are planned are given more authority to decide for themselves what the appropriate course of action should be. I believe that this in itself is a good thing, but it also means that we need to have in place *a procedure* that is regarded to be fair by all concerned for making these types of decisions. This also means that it is urgently necessary to strengthen the research ethics review procedures and the competence in research ethics both locally and internationally. Two ways this process can start would be to do the following:

- Examine existing ethics review procedures in countries where preventive HIV vaccine trials are being planned with a view optimize such issues as composition of the committees and operating procedures
- Establish a high quality training program in research ethics for people involved in HIV vaccine trials and ethics review procedures in the countries concerned

There is one further reason for strengthening the research ethics review procedures in cases such as these. As we have seen, a crucial part of the justification of these trials involves judgements about the possible benefits for the countries involved, and the lack of alternative ways of doing these trials. Researchers themselves often have exaggerated opinions about the possible benefits of their own research projects. There is not necessarily anything wrong in this. But the researchers' enthusiasm needs to be countered by critical questions about whether there really are no alternative way of doing the research. Doing this requires quite a high level of knowledge of the field of study, as well as knowledge about general issues in the methodology of clinical trials and current standards of research ethics.

6. CONCLUSION AND SUMMARY

This paper has argued that the general prohibition against carrying out phase III trials in developing countries but not in developed countries is not defensible. Trials which most, if not all, would find ethically unobjectionable have in the past been carried out in developing countries in this way, and there are circumstances, such as legitimate disagreement among experts, or legitimate differences in the evaluation of social risks, that would lead to legitimate differences of opinion concerning the acceptability of trials. There are also legitimate reasons for carrying out phase I and phase II trials in developing countries, but not in developed countries. I have also argued, however, that one should be aware of the controversial nature of arguments that accept a higher *individual risk* in developing countries for the sake of some future social benefit. I have also argued that, under certain conditions, one may justify trials in developing countries that can not be carried out in developed countries because of economic differences between the countries. One should again be aware of the controversial nature of these arguments, and, as the debate over the perinatal transmission studies has shown, many people will not accept these arguments. Such trials should only be carried out after extensive review, both locally and internationally, using a procedure that is regarded to be fair by all parties concerned. Furthermore, only in exceptional circumstances should such trials be carried out if they do not conform to currently accepted research ethics guidelines. Rather, one should attempt to achieve a broad consensus that changes in the guidelines are necessary before undertaking such trials.

One final note. This paper has had a somewhat narrow focus, discussing the various arguments for and against trials in light of current guidelines. I do believe, however, that one substantial conclusion can be drawn from the arguments presented in this paper, and that is that there is a need to revise the guidelines. The phrasing of the guidelines we accept today seem to prohibit trials in developing countries that reasonable people would find acceptable. Not only would reasonable people find these trials acceptable, but there are in fact strong reasons for encouraging more research and more research collaborations with developing countries. There is a need to build infrastructure for research, to develop expertise, and to carry out research that is addresses the types of problems found in developing countries. One could make the case that some of the currently accepted guidelines hinder, rather than faciliate, that development. This makes it even more urgent to review the procedures we accept today, and make appropriate revisions in the guidelines (I am indebted to Dr. Peter N. Mugyenyi for the points made in this paragraph).

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