RESEARCH SUBJECTS IN DEVELOPING AND DEVELOPED COUNTRIES SHOULD HAVE THE SAME STANDARD OF CARE

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Thank you Mr. Chairman.

Initially let me state that I am grateful to the organizers for the invitation to take part in this session, and I am highly honoured to share this debate with Prof. Benattar.

This talk is from the perspective of an NGO activist, a person living with HIV in Brazil, a Latin American and a Math PHD. Since we are more familiar with AIDS, this talk restricts itself to a discussion of this area.

During the next minutes I shall offer some arguments supporting that participants in clinical trials in developing and developed countries should receive the same standard of care. Many national Physicians Associations, such as the Brazilian, Dutch, German, Norwegian and Thai Associations currently support this position.

Distributive Justice and the Global AIDS Pandemic

A first argument against different standards of care refers to distributive justice and the globality of the AIDS pandemic. The principle of distributive justice could be stated as: those who bear the highest burdens should receive the highest benefits.

This means that if we have a trial which could be developed in two communities, one of them more vulnerable than the other, we should conduct the trial on the more vulnerable community ONLY IF it would receive a higher benefit than the less vulnerable community. For example, we should not develop a trial in a community of poor people when the main beneficiaries will be rich people.

This is clearly stated in some CIOMS guidelines (International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva 1993.)

Guideline 8 (CIOMS): Research involving subjects in underdeveloped communities. Persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities.

Guideline 10 (CIOMS): individuals or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed.

On the other hand, AIDS is a **global epidemic**. And certainly the result of many trials conducted in developing countries will benefit developed countries. This is not the case for all diseases, like dengue for example.

Therefore, a trial whose results would benefit mostly developed countries and which is conducted in a developing country should offer, among other things, **exactly** what would be offered if the trial were conducted in the community which benefits the most from it.

Let us give an example.

A recent trial on infectivity and viral load published recently in the NEJM 2000 (342): 13; 921-929 was carried out on persons in rural Africa and proved, in a secondary analysis, that infectivity was proportional to viral load. These persons were not provided ARVs, among other things. The people who take most benefit from the result of the secondary analysis are those who can control viral load, eg, people in developed countries in general. Those who bore the heaviest burdens will have the least benefits. "The very condition that justified doing the study in Africa in the first place - the lack of availability of antiretroviral treatment - will greatly limit the relevance of the results there. As is so often the case, the results will probably find their greater application in the developed world" Angell, M. Investigators' responsibilities for human subjects in developing countries. NEJM (2000) 342 (13): 967-969

In our opinion if the aim of this trial had been to prove the relationship between viral load and infectivity, it would not fulfill the principle of distributive justice.

One of the authors, when the ethics of this trial was questioned in an internet discussion [Treatment Access list, messages #791 and #792 argued that this trial "... provides a strong rationale for the development of affordable ARV treatments or therapeutic HIV vaccines, both to benefit HIV-

infected persons and to control HIV transmission..." We think that this assertion just confirms our thought.

The following questions might be interesting for the debate: Could an identical trial be conducted in a developed country? Could a trial designed to evaluate the same relation between infectivity and viral load be conducted in a developed country?

We think so, under certain more complex conditions. The complexity is due to the fact that we would have to satisfy optimal ethics and optimal scientific methodology.

Ethics and scientific methodology have different sources and in order to respect both, the research will often have to be more complex than if we only respected science. This is a common challenge, but we are confident enough that researchers can surpass it. "...In appearance, moral demands are a brake. In fact, they contribute to the best and most beautiful of what man has produced for science, the individual and the community..." Moral limits of Medical Research and Treatment, read before the First International Congress on Histopathology of Nervous systems, Pope Pius XII. (1952) apud Beecher, H JAMA (1 959), 466-478

Researcher-volunteer versus Doctor-patient

For our next argument let us initially quote parts of the Helsinki Declaration (1996, currently under review) which is important for our discussion:

The Declaration of Geneva of the WMA (1983) binds the physician with the words, "The health of my patient will be my first consideration"

Paragraph 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".

From here on, we shall refer to the best proven treatment as optimal treatment and any other inferior therapy will be called suboptimal.

One of the ways differences in standards of care in clinical trials occur is by the provision of suboptimal treatment to people in developing countries.

As some authors have observed, offering suboptimal treatment in clinical trials yields a conflict of interests between the relations "doctor-patient" and "researcher-volunteer". The doctor-patient commitment "...is governed by justice, altruism and virtue, not by efficiency neither marketplace values..." Brennan, Troyen. Proposed revisions to the Declaration of Helsinki: will they weaken the ethical principles underlying human research. **In Bull Med. Eth**. 1999; 150 :24-28. This relationship is based on "solidarity" (Weizsaecker apud Beecher 1959)

Physician researchers engaged in trials testing the efficacy of suboptimal treatments may find themselves in conflict of interests. This would be due to the fact that researchers-physicians may often have access through various sources, to medication that could be used to supplement the suboptimal treatment their trial patients are being subjected to.

But in this case the patient would have to be withdrawn from the research sample since he would have received different treatment from those being tested. To make matters more complicated, if the patient were excluded from the suboptimal treatment he might be reduced to the supplementary doses obtained by the reseacher-physician (which in themselves might be inferior to the original suboptimal treatment).

Moreover, let us observe that the research itself can get inadequate results from its volunteers.

This happens because the physician should inform his patient that there is an optimal treatment and that he will receive a suboptimal treatment. But, for the success of the trial, the physician must also ensure that the patient - even though accurately informed - does not, procure for himself a supplement to the trial medication.

Therefore for the success of the trial, not surprisingly participants should be chosen among those who do not have the personal possibility of getting supplements, that is, the more vulnerable the better for the rigour of the research and (allegedly) for the future benefit of the society.

An example is the case of the trials comparing short course AZT versus placebo. A researcher getting some extra bottles of AZT could provide them to some people in the trial. Or a participant if adequately informed by the physician and by the Term of Informed Consent about the existence of a better regime like the one offered by PACTG076, could get some extra bottles of AZT for herself or her baby.

Multicentre studies and differentiated standards of care

Does this mean that we are only allowing multicentric studies between countries which provide exactly the same standard of care?

The conflict between the interests of "the health of my patient" and "the rigour of my research" is clearly established, unless the trial provides the optimal intervention.

AIDS Vaccines Area

In the area of HIV vaccines, efficacy trials were planned since 1994, before the last revision of the Helsinki Declaration (1996). Why is it that nobody questioned paragraph II.3 in those days? Why is it that when those efficacy trials were planned no one thought about different standards of care, while nowadays an UNAIDS document suggests this possibility-UNAIDS Ethics Guidelines (16)? Why is it that these different standards of care appear in the AIDS vaccines area EXACTLY IN THE SAME MOMENT in which the US government invests more money on HIV vaccines, the G7 group commits itself to doing the same and when the World Bank seeks funds for these purposes? Multimillionary agencies and the richest countries in the world can offer the optimal therapy to infected participants - whose number need not be great for a vaccine to show some efficacy. For these reasons, the best known standard of treatment can be provided for people infected during the trial of HIV vaccines, either in developing or developed countries.

Tell me WHY

Why are we trying to establish different standards for participants in clinical trials according to the place in which the trial is conducted?

Why is this question posed now? And why does it specially derive from the AIDS area? Why does this question appear after a Conference was held in Geneva with the motto "Bridging the Gap", obviously addressing the treatment gap? Why are we now trying to widen the treatment gap by including a population which until now clearly had access to treatment, ie, volunteers in a clinical trial? Why is it that in the Vancouver Conference we had as a motto "One world, one hope" (Vancouver, 1996) and now we propose two or much more worlds?

I think that many authors have already addressed this subject:

"It is the rapid march of science itself that is largely responsible for the pressures to weaken subject protections. Capability tends to be at odds with restraint... These increased capabilities are generating demands for ever-larger numbers of human subjects in research, for easier recruitment and conscription of research subjects", Challenges to Human Subject Protections in US Medical Research. Woodward, W. JAMA (1999) 282 (20): 1947-1952

(*)"We feel that one of the main issues we all have to face is the increasing, almost dominant role that pharmaceutical company sponsorship is now playing in the conduct of clinical studies. ...How does one make sure that such commercially funded research, involving secondary gain on the part of the sponsor and partner-researcher is ethically and scientifically sound?"A comment from Thailand (SP, HW, CP and YT) In **Bull Med. Eth**. 1999; 150: 37 (*)

In the US, "... recent, widely reported problems in clinical research have shaken public trust..." which led to a "Reaffirmation of Trust Between Medical Science and the Public" (June 7th, 2000) undersigned by more than 300 Universities and organizations in the US. This Reaffirmation states, among other things, that "... the health and welfare of patients must always be placed above all other concerns,..."

The reasons quoted for conducting research in developing countries rather than in developed ones are: "... **lower costs, lower risk of litigation, less stringent ethical review, the availability of populations prepared to give unquestioning consent**, antecipated underreporting of side effects because of lower consumer awareness, the desire for personal advancement by participants, **and the desire to create new markets for drugs**." (emphasis added) Research and Informed Consent in Africa - another look. Ijsselmuiden, Carel B. NEJM (1992) 326 (12): 830-834 and Temmerman M. Informed Consent in Africa. NEJM 1992; 327: 1102-3 apud Peter Wilmhurst. Scientific Imperialism BMJ 1997; 314: 840-841

But another source of arguments to provide suboptimal treatment in clinical trials is also that there is a need to test cheaper treatments affordable in developing countries. Certainly my colleague will address this point with brilliance.

In these trials the importance of the care of research subjects is secondary to the importance of the results and the accessibility of the treatment at large. These trials are being held "for the good of society". Celebrated authors such as Beecher, state that a trial is ethical or not since its inception; the ends do not justify the means. This is my conviction.

But let us stress that many of the benefits of these trials are not accessible to the target population yet. An example is the trial on short course AZT in South Africa for pregnant women with HIV, where wide access to it is long due and authorities do not even recognize the relation between HIV and AIDS. What about participants who join the trial taking into account that there will be a benefit for their communities? For this reason, "Ethics and basic human rights require not a thin promise, but a real plan as to how the intervention [to the population] will actually be delivered are needed" Annas, G.J. and Grodin, M. A. Human Rights and Maternal-Fetal HIV transmission Prevention Trials in Africa. Who should require this: the researchers, the local IRB, the foreign IRB? Who is responsible, accountable, liable?

Can we perform these trials because they can be used to provide a stronger argument to present to national authorities?

This would mean that any cheaper treatment than the best treatment could be tested since some time some authority may be sensitive to it. This is only marketing policy.

(*)An author asks "... [if access to AZT for pregnant women does not exist yet] So, why are these trials undertaken? My assessment is that since placebo trials could no longer be conducted in the USA or other developed countries, there was still an interest in knowing whether cheaper regimens would be effective. So the only people who will benefit will be people in developed countries, and the few mothers who receive AZT and not placebo in the trials [since pregnant women with HIV do not even have access to it] ". Laing, R. If a lower dose was effective, would it make any difference, Procaare 13, October, 1997(*)

Approval of clinical trials of suboptimal interventions on the basis of the future availability, may raise some problems for the IRBs of the developed countries involved.

According to **Guideline 15(CIOMS)**: Obligations of sponsoring and host countries "...An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the **ethical standards should be no less exacting than they would be in the case of research carried out in that country...**" (emphasis added)

Since they do not provide the same standard of care, how can this approval be obtained? Some authors say that the ethical principles can be the same, but their expression varies locally. Ethics and international research. Halsey, N. et al BMJ (1997) 315: 965-966

Certainly the 1981 Guiding principles for Human Studies at the Massachusetts General Hospital are not the same principles since "concern for the individual takes precedence over the interests of science and society" and "A study is ethical or

not at its inception; it does not become ethical because it succeeds in producing valuable data." Guiding principles for Human Studies. Boston: Massachusetts General Hospital, 1981.

On the other hand, in the Rakai study, negative HIV partners in discordant couples were not informed by physicians on the status of their spouses, something that they would have to do in developed countries (the US?). What kind of ethics principles permits opposite behaviour in this context?

Other Resolutions related with the right to life and health, and the principle of equality.

We must recall that access to life (Art III) and health (Art XXV) are parts of the Declaration of Human Rights undersigned by every nation in this planet. This is the reason why many Medical Associations argued that accepting different standards of care in the Helsinki Declaration "...would mean to preserve inequality as a principle in the most important set of principles that regulate research in human beings. Equality and justice are a central part of all Human Rights Declarations and are widely acceptable as central principles." (British Medical Association. Com-Helsinki-Oct 1999)

Recently the Mexican Supreme Court ruled in a unanimous sentence that the right to health is not satisfied by providing some drug or some medical care. Rather the best therapeutic alternative must be provided, defined as the one which results in the best quantity and quality of life (Amparo 223/97). This should be compared with the recent draft for the Declaration of Helsinki (May 4th, 2000), where instead of the "best proven" treatment only a "proven" treatment could be offered.

(*) Further, neither the recent discovery of such treatments nor the existence of other illnesses that deserve the same or more attention can constitute an obstacle for this right since these matters are irrelevant on the right of an individual to receive treatment for his illness. (*)

Hence, we stress that the right to optimal care is universal, but unfortunately it is not provided everywhere. Nevertheless this is no reason for that right to cease, and it would be sophistical to deny the fulfillment of this right if we have the resources to do so, as is the case in the AIDS Vaccines area. Paraphrasing an author: Would you forbid people in developed countries from using triple therapy because most people in the world do not have access to it? Why do we simply accept these borders as natural restraints to our health rights? (Chris Green, Indonesia, A response to Richard Laing, Procaare, October 17, 1997)

Undue Induction and Coercion

Some contend that even in case we had the money to provide the optimal care to participants, we should not do so because this could be undue inducement or even coercion.

Enjoying the right to life (without harm to others) cannot be coercive, because the right to life precedes all other rights.

Following this kind of reasoning, couldn't we argue that conducting an unethical trial (with different standards than those in developed countries) in a country extremely afflicted by AIDS, (*)offering some future benefit of access to the product if shown efficacious (*) is also **undue inducement or coercion on the country** to participate in these trials ?

A Suggestion

The subject we are discussing can be examined as an equation:

standard of treatment in developing countries must be = to standard of treatment in developed countries

I believe that in a clinical trial II.3 of the Helsinki Declaration has to be respected. (*)"Thus, scientific research does not admit any inequality among participants in clinical trials. And it also states implicitly equipoise, that is "a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial" "Freeman, B. Equipoise and the ethics of clinical research, NEJM 317(3);141-145 In this case the trial could be conducted in any country. (*)

But in order to continue the discussion let me propose the following idea: During an academic meeting, in a discussion about testing a subtype B vaccine in South Africa, some people from developed countries saw no obstacle to test a vaccine constructed on a subtype which is not the prevalent in South Africa. A colleague from South Africa did not agree and she just returned the question: would you agree to test a subtype C vaccine in the US or Europe, where this subtype is not prevalent?

That is, to test a subtype B vaccine in South Africa would be **as ethical as** testing a subtype C vaccine in the US or Europe.

Returning to the equation, let me stress that it does not establish any standard of treatment at all, only **an equality of standards**. A way to evaluate exploitation in a clinical trial is verifying whether equality holds or not: if it does not hold then we may be in the presence of exploitation.

Inspired by her assertion, my suggestion is that whenever the best proven treatment is not provided in a trial in a vulnerable community then **the trial must be matched**, that is, **there will be an identical trial in population, standard of treatment, endpoints, etc, being conducted simultaneously in a developed community.**

Conclusion:

I think that the problem is mostly of access to treatment and prevention. Not access to trials, and even less to unethical trials. The International Covenant on Economic, Social and Cultural Rights (Art. 2.1, Res. 2.200-A XXI UN General Assembly, December 16th, 1966) established the need to **progressively** achieve "...the full realization of the rights...". Here we are not progressing. It is not through reductions of rights of the most deprived and the consolidation of inequalities that we shall obtain better health for all and more dignity for the human being.

(*)"We believe that much of the debate in the past few months is the result of an unrecognizable confusion about the role of clinical research in a public health crisis. Although clinical research may be justified by such a crisis and is indeed expected to contribute to its solution, it is not in itself the solution. Research in developing countries proved years ago that vitamin A supplementation could decrease infant mortality by 30% and that a vaccine could prevent the perinatal transmission of hepatitis B, and yet, these lifesaving, cost-effective, public health interventions are still not available in the countries that need them most. No one can guarantee that the discovery of an effective, easier-to-use, more affordable method to prevent perinatal HIV will lead to its widespread application. This sad reality mandated that human subjects, particularly the politically and economically vulnerable, as well as those who cannot provide consent - children in this case - should be protected during research. Indeed, as recently as last year, the good-practice guidelines recommended by the International Conference, on Harmonisation restated that the researcher's primary ethical responsibility is for the welfare of subjects participating in the research, not for the welfare of future patients who may benefit from it." Lallemant, M et al. Letter to the Editor NEJM (1 998) 338(12):836-844(*)

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I would like to end by quoting from two African authors who while referring specifically to the African situation, also depict the Latin American reality.

"Until the educated use their links with Western institutions and research centres for the benefit of the mass of Africans, rather than for ephemeral dollars, unethical research will go on in Africa. Africa's problem is not that of resources. But of priorities misplaced." The response of People with conscience , Oyewale Tomori, Procaare 13, October, 1997.

"Unethical research will not benefit developing countries in the long run, since it undermines human rights, which are the very foundation on which sustainable development needs to be built. In addition, it violates the principle of justice that a continent impoverished through colonialism, and forced to continue to be unable to provide gold-standard treatment because of debt traps, will continue to provide the human laboratory where placebo-controlled trials can be conducted because locally affordable care is often no more than placebo treatment." Ijsselmuiden, Carel B. Letter to the Editor NEJM (1992) 338 (12): 836-844

Thank you