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January 15, 1999

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Re: Comments on Guidance Document on Ethical Considerations in International Trials of HIV Preventive Vaccines

Dear Jose:

The elaborate, time-consuming and expensive UNAIDS consultation on the ethics of HIV vaccine trials seems about to come to its pre-ordained conclusion: in areas of little disagreement, existing standards on the ethical conduct of clinical trials are simply reiterated; in areas of controversy, the Guidance Document in effect provides researchers with a blank check to proceed as they would without the consultation, abrogating existing ethical doctrines, as long as they can convince local researchers to go along. This is not what we had hoped would come of this process; for these reasons and others set forth below we do not endorse the document.

We are further dismayed that the final draft Guidance Document has been sent for comment only to those attending the final consultation meeting in Geneva on June 25 and 26, 1998, and not to those attending the regional workshops in Uganda, Thailand and Brazil, or to those attending the meeting in Washington, DC, USA, as was promised at the Geneva consultation meeting. To add insult to injury, many of the recommendations of the regional workshops have been ignored. We request that the Guidance Document not be finalized until those present at the regional meetings, in particular, have the opportunity to comment.

This Guidance Document should be viewed in its proper historical context: as part of a multi-pronged assault on the ethical standards established in such documents as the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) (proposed changes to these documents are the other prongs of the assault). The result, for the most part, will be a weakening of protections for research subjects in developing countries, opening them up to more exploitation as research increasingly becomes international. There could be no worse time for such a retrenchment.

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It is precisely this historical context and the discounting of the regional workshops that convinces us that the outcome of the Guidance Document was preordained. If UNAIDS wished to maintain the appearance of objectivity, why did it select Dr. Robert Levine of Yale to write the Guidance Document, even though he has been heavily involved in efforts to weaken human subjects protections in the Helsinki and CIOMS documents and was known prior to the Consultation to be hostile to providing subjects with appropriate treatments or preventive interventions in clinical trials. As Claude Raines might have said: "Round up the usual ethicists."

The manner in which the public relations aspects of the Geneva meeting was handled further supports the notion that the results of the Consultation were preordained. In separate fora, the Consultation was depicted as reaching consensus on the issue of the treatment of HIV-infected subjects, even though the Guidance Document was still in draft form, and in each case an embarrassing retreat was forced. First, UNAIDS put out a press release on June 29, 1998, immediately following the Geneva ethics meeting, trumpeting the "consensus" that had been reached at the meeting (there was no such consensus, as indicated below), even though the process was not completed. This prompted a letter of protest by nine Geneva meeting attendees (including one of us, PL) from around the world, leading to UNAIDS' removal of this press release from its web site in the Fall of 1998. Second, in the closing ceremony of the XII International Conference on AIDS, which immediately followed the Geneva ethics meeting, Dr. Catherine Hankins stated that a consensus had been reached in favor of the "highest practically attainable" standard (see below for further discussion of this term and its implications). This created so much controversy that the text on UNAIDS' Conference web site[1] had to be revised.

The Guidance Document seeks to sugarcoat the multiple areas of intense conflict that were apparent not only in Geneva, but also at the regional meetings. In particular, the decided lack of consensus over the issue of whether people who become HIV-infected during the trial should receive antiretroviral treatment, reflected in the differing opinions between the regional workshops[2] and in heated discussions at the Geneva meeting, is handled by a. putting forward a procedural standard, when a clear substantive standard is called for; b. relegating the crucial definitions of the different options considered by those involved in the consultation to the Glossary; and c. not stating that one of the three treatment options (the "standard of care" option) was clearly rejected at the Geneva meeting.

Let us be clear on what happened at the Geneva meeting with regard to this contentious issue. Three potential levels of care were put forward: 1. Standard of care; 2. Highest attainable therapeutic method; and 3. Best proven therapeutic method. Option 1 was rejected by consensus, but the Guidance Document does not make this clear. This means that, as the Guidance Document now states, the care provided should be no lower than the "highest attainable therapeutic method." Much debate ensued between whether to endorse options 2 or 3 and, as reflected in Dr. Hankins' corrected remarks as well as articles in Science[3] and the New York Times,[4] there was no consensus as to which of these options to favor. In its stead, a procedural solution was put forth at the very end of the meeting and was not extensively debated. This procedural solution was that the level of care provided should be decided by the host country, in

collaboration with the sponsors. While on the face of it this may seem reasonable (we believe this is why there was no debate over it), when combined with the lack of consensus over options 2 and 3 and the fact that many are likely to quickly interpret option 2 as meaning that antiretroviral therapy cannot be provided in most likely host countries, this is a *de facto* devolution to the rejected option 1. (Indeed, at the Washington meeting, Dr. Jack Killen of NIH asked whether option 2 could in certain circumstances be equated with option 1.) The result will be that as long as sponsors can identify a willing host country, researchers will have the Guidance Document to back them up in their withholding of known effective therapy, in direct defiance of CIOMS and the Declaration of Helsinki. Of course, this is what many researchers had hoped would come of this process. This decision renders the entire consultation process futile, at least inasmuch as it applies to this most-crucial issue. For if all that has been decided is that the host country should decide, what has been accomplished? Was there ever any question that these two parties would be involved in this decision? What this does is effectively remove UNAIDS or other similar body from the process of making this decision. The purpose of guidelines is not to abdicate responsibility for the most difficult decisions.

It is particularly galling that there is not even any attempt in the Guidance Document to justify this significant departure from the current governing ethics documents. Even though this Guidance Document is occasioned by the need for clear guidelines specifically for the ethical conduct of HIV vaccine trials, the Preamble does not even bother to explain why the specific circumstances of the HIV epidemic merit a departure from the existing guidelines. (This further convinces us that the intended reach of the Guidance Document is broader than the context of HIV vaccine trials.) It is not until page 8 of the 15-page Guidance Document that we encounter material that is HIV-specific.

The Guidance Document fails to even consider alternative study designs to the withholding of effective therapy. Why does the Guidance Document depart from the governing ethics documents without even a discussion of whether viral load measured shortly after seroconversion, an accepted predictor of progression of HIV disease,[5] could be used as a proxy measure, facilitating the provision of antiretrovirals? This issue was raised both in our presentation at the Washington meeting and by participants in the Brazil meeting.[6] And why does the Guidance Document simply accept arguments that providing antiretrovirals will make it impossible to detect vaccine efficacy in delaying the progression of disease when it is clear that antiretrovirals reduce rates of progression but do not eliminate progression? Why were no sample size estimates even examined to see the likely impact of antiretrovirals? Again, the purported needs of researchers have taken precedence over the need to protect human subjects.

We now provide specific comments on the draft Guidance Document.

Page 3, Preamble

Astonishingly, the Preamble to this ethics document actually puts the need to develop the vaccine before the need for human subjects protection. In contrast, the Uganda meeting concluded, "No

phase 3 trial should be conducted on the basis of desperation and urgency alone."[7]

As mentioned, the Preamble fails to provide any justification for why we even need a specific Guidance Document for the ethical conduct of HIV vaccine trials. We believe such justifications exist: vulnerability of the populations to be studied, researcher conflict of interest, false-positive antibody tests, social discrimination, behavioral disinhibition, etc.[8]

Paragraph 2: "This document is not legally binding; however, it may serve to suggest standards and processes for arriving at local standards." This immediately establishes the idea of differing standards between countries, when the purpose of international guidelines should be to create universal standards, where possible. We suggest: "however, it may serve to suggest standards and processes for resolving the difficult ethical issues that attend HIV vaccine trials."

Page 4, Preamble

Paragraph 3: The discussion of "protectionistic attitudes" and "excessive paternalism" is a form of editorializing that has no place in what are supposed to be practical guidelines on how to conduct ethical trials. Again, this leads us to believe that other motives are operating. The final paragraph in the Preamble should therefore be eliminated.

Moreover, this section arrogantly suggests that abrogations of the rights of subjects in developing country trials are safely behind us. Have we already forgotten the relatively recent vaccine studies of Dr. Daniel Zagury in which Zairian children were injected with a putative HIV vaccine, leading to several deaths, without adequate informed consent? (A source close to the group told the New York Times that a major reason the trial was conducted abroad was that it "was easier to get official permission [in Zaire] than in France."[9]) Or the lack of adequate informed consent in the CDC perinatal study in Cote d'Ivoire?[10] Or the lack of adequate informed consent in the Case Western isoniazid study in Uganda?[11] History should have taught us not to be so complacent.

The Guidance Document also ignores the nature of the power dynamic inherent in any research undertaking in a developing country trial with an industrialized country sponsor. This applies to the negotiations between the host country and the sponsor and to Institutional Review Board (IRB) oversight. As one observer in Kenya noted about local IRBs: "The membership consists of interested parties, such as the investigators, and they may receive incentives, including coauthorship or a ticket to an international conference. This is a serious conflict of interest ..."[12]

The power imbalance is relevant relevant to the informed consent process itself. As a Zimbabwean virologist who wrote to us in the context of the controversy over the AZT perinatal trials said: "In an environment where the majority can neither read nor write and is wallowing in poverty and sickness, hunger and homelessness, and where the educated, the powerful, the rich or the expatriate is a semi-God, how can you talk of informed consent?" Rather than acknowledging these on-the-ground power dynamics, the authors of the Guidance Document

would rather hide behind such meaningless slogans as protectionism and paternalism.

Page 5, Vaccine Development Program

There is really nothing in this section that is HIV-specific. One item that should be included, since it was widely agreed upon at the Geneva meeting, is the need for vaccines against the local clades (not simply "a virus that is an important public health problem in the host country.") While the extent of cross-reactivity between viral clades may not be completely resolved at the present time, it is inarguable that the subjects cannot be worse off if the vaccine being tested is actually directed against the local clade.

Page 7, Consultation with the Community

Paragraph 2: The Guidance Document now states that consultation with the community should "preferably" occur before the protocols are finalized. There is no reason for the qualifying word "preferably." The process of considering whether to conduct a study and the process of drafting a protocol is one that takes many months and even years. This is more than enough time to consult with the community in a meaningful way.

Paragraph 4: The Guidance Document appears to permit investigators to conduct community meetings at which the study is described and then have the subjects provide informed consent at the same meeting. This practice should not be endorsed, as it creates a coercive environment in which it will be difficult for subjects to decline enrollment. Furthermore, this erosion of human subjects protections seems unnecessary; many (probably most) studies in developing countries have obtained informed consent on an individual basis without doing so in the context of a community meeting. We would have no objection to community meetings (indeed we would encourage them), as long as the subjects do not provide their consent at the meeting.

Page 8, Informed Consent

Paragraph 3: As was clearly agreed at the Geneva meeting, a comprehensive intervention seeking to prevent HIV transmission (including, as appropriate, sexually transmitted disease treatment, condoms, sterile syringes, and education), not simply "counseling," is required.

It has been widely accepted for years and was clearly noted at the Thailand meeting[13] that subjects need to be informed that they will test positive on some HIV antibody tests and may be subject to discrimination in employment, insurance, health care, housing and ability to travel as a result. This is not mentioned in the Informed Consent section of this Guidance Document. In addition, it is critical that the researchers go beyond mere informing to actually seeking ways to minimize the likelihood of such discrimination. Concrete suggestions about how to do this (e.g., meetings with insurance companies prior to the trial, provision of a card that explains that the bearer is a subject in a study and may falsely test HIV-positive as a result, as has already been done with some success,[14] provision by the sponsor of confirmatory testing for those with

vaccine-induced seropositivity, as endorsed in the Thailand,[13] Brazil[6] and Uganda[7] meetings) are precisely the elements that should be included in any HIV vaccine ethics document. The Uganda meeting arrived at the following consensus: "Preventive steps should be taken, through advocacy, creating protective legislation and ensuring its enforcement. Measures such as providing a card to the participant which explains a vaccine-induced positive status may also be helpful."[7] Yet this Guidance Document makes no mention of vaccine-induced seropositivity, let alone methods to ameliorate the problem.

The Guidance Document fails to either recognize or provide recommendations to reduce the social discrimination likely to ensue from simply being enrolled in an HIV vaccine trial. To be in such a trial is to invite being identified as sexually promiscuous, homosexual, an injecting drug user or a sex worker.[15] Most of these are illegal in many countries, developing or developed. As the Thailand regional meeting concluded: "There is significant risk of discrimination for participants in HIV vaccine trials in any country. Proactive efforts should be encouraged prior to a trial beginning in order to prevent discrimination."[13]

Page 9, Children

Paragraph 2: "Unless exceptions are authorized by national legislation, the consent of the minor's parent or guardian must be secured ..." As a general matter, there is no reason to accept broad national exceptions to the requirement that a minor's parent or guardian provide informed consent. Where national legislation provides more protection (a possibility acknowledged in the next sentence), acceding to local law is acceptable. But where local law is insufficient to adequately protect subjects, such exceptions should not be authorized. (If, on the other hand paragraph 2 is referring to the kinds of exceptions noted in paragraph 3, we would not object; but then the first sentence in paragraph 2, which is written too broadly, can safely be omitted.)

Page 10, Pregnant and Breastfeeding Women

This section needs a paragraph addressing the ethical responsibilities of researchers should the woman contract HIV infection. Will the Thai AZT regimen be provided to all HIV-positive pregnant patients (it should be)? These women should, at a minimum, receive interventions consistent with UNAIDS' current recommendations on breastfeeding.

Point 3: Damage to infants (or others) caused by the vaccine should be compensated by the sponsor. The current language is so vague (it doesn't even distinguish between damage caused by the vaccine and damage that can be expected or foreseen) that it would allow wealthy pharmaceutical companies and industrialized country research funders such as WHO, NIH and CDC to pass the bill for damage caused by an improperly manufactured vaccine on to developing countries, in violation of the CIOMS document which requires the sponsor to pay. Particularly because the costs of such compensation in the developing country context are likely to be limited, we can see no reason for this retreat.

Page 10, Researchers' Obligation to Reduce Risk for Trial Participants

This section is missing a discussion of why these risk-reduction efforts are necessary. The standard obligations of researchers to protect subjects are amplified in the context of HIV vaccine trials where it is quite possible that subjects will engage in higher levels of risk behavior once they enroll in the trial. Such a disinhibiting effect has already been demonstrated in a small study in San Francisco, with levels of counseling and informed consent that will likely exceed what can be offered in studies in developing countries with thousands of subjects.[16] This point was made several times in Washington and in Geneva, at the least (we did not attend the regional meetings), but is missing from the Guidance Document.

Final sentence: "Risk reduction efforts should be evaluated in terms of their success in producing informed decision makers rather than simply in lowering the rate of either high-risk behavior or infection among trial participants since the goal of counseling is to enable people to make choices in the light of relevant facts and not to force them to make particular choices." This sentence is unnecessary, is not reflected in the summaries of the regional meetings where it seems not to have even been raised,[2] was not endorsed in Washington or Geneva, and should therefore be omitted. In addition, it is slanted in ways that do not encourage researchers to make a substantial effort to reduce the risks of transmission. The goal of risk reduction is to have as many HIV-negative subjects as possible; this sentence makes it seem as if an informed, but HIV-positive subject, would be equally acceptable.

Although the inclusion of an acknowledgment of the researchers' conflict of interest (it is not "potential," it is obvious) is important, it is not as useful as recommending the approach that would solve the problem: requiring impartial, well-trained individuals without a direct interest in the trials' outcome to conduct the risk-reduction efforts.[17] This idea received significant support in Geneva and should be included in this Guidance Document.

Page 11, Antiretroviral Prophylaxis in Cases of HIV Exposure

Paragraph 1: The strong statement in the final sentence about not using the possible effect of post-exposure prophylaxis upon the number of end-points as a reason to not provide PEP should be repeated in the next section addressing researchers' obligations to provide treatment to subjects who become infected during the trial. This point was made forcefully at the Brazil meeting: "It would not be ethical to deny counseling, post-exposure prophylaxis or antiretroviral or other treatment to participants solely for the purpose of making a vaccine trial more valid or statistically powerful."[6]

Page 11, Treatment of HIV Infection Acquired During the Conduct of a Vaccine Trial

This remains the most problematic part of the Guidance Document as, in most cases, it will consign developing country subjects to no treatment or treatments known to be inadequate. It is only on close perusal of the Glossary that the Guidance Document's true meaning and

insidiousness become clear. Although we continue to assert that the need to weaken the CIOMS and Helsinki documents has not been demonstrated and to insist that double standards in HIV vaccine trials are unacceptable, this section should at least more closely reflect what actually happened at the regional meetings ("The regions differed widely between each other on whether participants who become infected during the course of the trial should be provided with HIV treatment if it is not generally available in the host country."[2]) and in Geneva. The Glossary definitions should appear in the body of the document, the fact that the "standard of care" option was rejected should be noted, as should the lack of consensus over the recommended level of care in Geneva and at the regional meetings.

The Guidance Document also skirts such important issues as who would pay for the treatment (we would argue the sponsor) and for how long the treatment would be provided (we would argue for the rest of the person's life to avoid cutting the subject off antiretroviral drugs and increasing the probability of developing resistant strains.)

At the Geneva meeting, the issue of intellectual property rights was removed from consideration, despite the protests of numerous attendees, primarily from developing countries. Yet intellectual property was a prominent focus of discussion at all of the regional meetings. (Brazil: "It may be reasonable for the host country to claim a right to intellectual property if its participation in the trial is deemed essential for the development of the particular candidate vaccine."[6] Thailand: "The case of HIV vaccines challenges [the practice of the sponsor retaining intellectual property rights], and there may be a rationale for the host to claim some portion of the right to intellectual property."[13] Uganda: "In general, an HIV vaccine manufacturer will have claim to intellectual property (patent and trademark). However, there may be situations in which the contribution of the host country to the vaccine development process is significant enough to justify the country having claim to intellectual property."[7]) In all three workshops it was agreed that "The contribution of host countries to the success of HIV vaccine trials is substantial, and thus requires that discussion on claim (sic) to intellectual property for a specific trial be carried out prior to the trial and be specified in the contract."[2] None of this is reflected in the Guidance Document. The difference between the "best proven therapeutic method" and the "highest attainable therapeutic method," as the Glossary attests, is primarily an economic one. The exorbitant prices of many drugs and vaccines relative to developing country budgets are in turn intimately connected to patent and trademark protections. As long as the Guidance Document is willing to substitute economic arguments for ethical ones in denying subjects access to antiretroviral treatment, intellectual property rights are a legitimate subject for this document. One cannot have it both ways.

What is striking here is how the Guidance Document is willing to accept the highest standards of health care in every respect except this: in the levels of risk-reduction interventions, in the care to be provided to those injured by the vaccine, in providing vaccinations unrelated to the study itself (Page 11), even potentially in post-exposure prophylaxis. How, then, can substandard medical care be countenanced in this area, the area of potentially greatest benefit to subjects?

The present Guidance Document creates the incentive for investigators to conduct research in the most impoverished areas, a possibility recognized by those attending the Uganda meeting, who concluded: "It is not ethical to conduct a trial in a given population solely for the purpose of avoiding populations where early treatment is used."[7]

Page 11, Control Arm of Phase III Vaccine Trial

Paragraph 1: We presume that this section is supposed to refer to using an HIV vaccine as the control arm. (Non-HIV vaccines in the control arm are discussed in Paragraph 3 of this section.)

Paragraph 2: Once again, the Guidance Document undermines existing ethics guidelines by permitting the use of placebos when known effective regimens exist. In point (c) of this paragraph, the poverty of the subjects is listed as a "compelling reason" to withhold a known effective vaccine from the comparison group. Providing second class medical care to people because they are poor is inconsistent with any modern notion of human rights. (Imagine if this were done to poor people in a developed country.) Our objections here are similar to those regarding the obligation to provide treatment. The Guidance Document is so intent on providing *carte blanche* for researchers that it doesn't even list possible alternative designs, such as equivalency studies, an issue raised at all three regional meetings.[6,7,13] In its haste to lower standards, it removes incentives for researchers to do a better job in protecting their subjects by considering alternative designs. As the attendees at the Thailand meeting concluded, "It was suggested that the scientific community may rely too readily on the power of randomized placebo-control trials, and that there needs to be encouragement to consider other study designs that could provide adequate data without the risks inherent in randomization."[13] This Guidance Document provides no such encouragement.

This betrays the Guidance Document's hidden assumption that conducting an ethically optimal trial is inherently at odds with a scientifically optimal one. With a bit of creativity, very often one can have both. The purpose of the Guidance Document should be to challenge researchers to design the best trial from both a scientific and ethical perspective. Instead, the Guidance Document permits the dismantling of human subjects protections for the supposed greater scientific good, without even bothering to offer an argument that this is necessary.

Furthermore, the three regional meetings are again ignored. As the summary of the regional meetings makes clear, "The use of a substance in the control arm of an HIV vaccine trial that is not active in preventing HIV is ethical as long as an effective vaccine is not known (emphasis added)."[2] (There was some debate over the definition of "effective.") The current language is inconsistent with this consensus. (This issue was not debated in any significant way at either the Washington or Geneva meetings that followed the regional ones.)

Paragraph 3: It seems here that the Guidance Document's authors have actually felt a few pangs of guilt in their denials of known beneficial treatments to people based on their poverty. To compensate, they now put forth offering non-HIV vaccines to subjects in ways that either are not

ethically required or are scientifically questionable. The requirement to provide the "best proven therapeutic method" is not limitless; it is confined to the diseases under study. (If Helsinki or CIOMS can be read to imply otherwise, this would be a legitimate reason to revise them.) There is no requirement to provide tetanus vaccination in an HIV vaccine trial, if tetanus is not the focus of the trial. To provide it to only one arm of the study even undermines the utility of the control arm, as strictly speaking one then has a trial of the relative efficacy of an HIV vaccine vs. a tetanus vaccine in preventing HIV transmission.

The Guidance Document is willing to go beyond the ethically necessary to reward subjects, as long as the researchers believe that this will not undermine their ability to measure the study outcomes. This is called a conflict of interest.

Page 12, Monitoring

This section is extremely vague and could be used to not adequately monitor informed consent. As was pointed out by many at the Geneva meeting, informed consent is often inadequate, particularly in developing country studies. Why not, as suggested in Geneva, require the investigators to actually confirm that adequate informed consent has been obtained and to take corrective action if it hasn't? In the absence of concrete guidelines, the monitoring of informed consent will probably be reduced to monitoring the paper trail.

The same is true for monitoring of the risk-reduction efforts. But the best protection in this case will not come from improved monitoring (which we also endorse), but from requiring an outside group to provide the intervention.

Page 13, Availability of Vaccines after Licensure

While we agree that the trial participants should receive any vaccine proved safe and effective, the Guidance Document is likely to ensure that the broader community gets short shrift. This is because the reader is instructed to interpret the Guidance Document as applying primarily to trial participants: "... the International Ethical Guidelines should be interpreted as follows: any HIV/AIDS vaccine demonstrated to be safe and effective should be provided to all participants in the trials in which it was tested." This is followed by a discussion of availability of the vaccine to the broader community that has few teeth (not even a suggestion that the agreement on post-trial availability should be in writing). If a document as influential as this one is likely to be cannot make a forceful case for the need for significant post-trial availability, it does not seem likely that pharmaceutical companies will feel pressured to provide this. Instead, the Guidance Document offers a discussion of the need for financial incentives for vaccine development that has no place in an ethics document. This Guidance Document is supposed to ensure optimal protection for human subjects, not "excessive protectionism" for multinational drug companies.

This is in marked contrast to the heavy emphasis placed on this issue in all the regional meetings: "All regions agreed that the historical examples of 'developing country' participation in vaccine

research where access to the final product has not occurred must not be repeated in HIV vaccine research ... Potentially, the product should also be available to other developing countries."[2] In addition, the helpful suggestions on how to maximize availability offered at the Thailand meeting[13] and by Dr. Natth at the Washington meeting are not reflected in the Guidance Document.

In sum, this is an extremely disappointing product of a lengthy, expensive process that could have provided useful guidance on how to best protect subjects in HIV vaccine trials. The input of the three regional meetings has been de-emphasized and in its stead there is overemphasis on the Geneva meeting, a meeting at which researchers were over-represented and developing country representatives were relatively under-represented, due to the costs of travel and accommodation. In addition, many developing country representatives were at a linguistic disadvantage.

In an area that for a number of specific reasons (vulnerability of the populations to be studied, researcher conflict of interest, false-positive antibody tests, social discrimination, behavioral disinhibition, etc.) cries out for increased human subjects protections, the Guidance Document instead represents a significant erosion of protections included in the current ethics documents. Indeed, as we have noted, the wider purpose of this Guidance Document seems to be to use it as a stalking horse for revisions of the CIOMS document and the Declaration of Helsinki.

We reiterate our commitment toward identifying a safe and effective HIV vaccine available internationally. But we cannot endorse a Guidance Document that is prepared to so unthinkingly roll back existing protections in the effort to do so, particularly because the burden of these reduced protections is likely to fall disproportionately on residents of developing countries. For in so doing, the Guidance Document is a dramatic departure from WHO's mission statement: "The objective of WHO is the attainment by all peoples of the highest possible level of health." If we cannot accomplish this even in the unique environment of multi-million dollar clinical trials for HIV, the future is very bleak.

Yours sincerely,

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Sidney M. Wolfe, MD
Director

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