FOUR FORWARD-LOOKING GUIDANCE POINTS

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Abstract

Four key guidance points in the UNAIDS guidance document, Ethical Considerations in HIV Preventive Vaccine Research, are compared with analogous statements in three other recently issued documents dealing with international research. Those documents are: the Declaration of Helsinki, as revised in 2000; the report of the U.S. National Bioethics Advisory Commission, issued in 2001; and a current (2001) draft revision of the 1993 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects. The four guidance points compared with statements on similar issues in the other three documents are Guidance Point 2, which deals with making available a safe and effective vaccine after trials are completed; the second half of Guidance Point 4, which requires that the desired outcome should potentially benefit the population from which research participants are drawn; Guidance Point 11, which discusses what should be provided to a control group in a vaccine trial; and Guidance Point 16, which addresses the care and treatment to be provided for trial participants who become infected with HIV during the trial. The analysis and comparison concludes that the UNAIDS guidance points are at least as ethically sound as analogous points in these other documents, and for the most part are ethically superior in providing greater benefits to research participants and to others. Nevertheless, they are subject to the criticism that they are too ‘aspirational’ and not sufficiently ‘pragmatic’.

The past three years have seen a flurry of activities devoted to international collaborative research conducted in developing countries. The UNAIDS guidance document, Ethical Considerations in HIV Preventive Vaccine Research, is one of four recently
issued documents addressing an array of similar issues. In this paper, I examine four of the 18 Guidance Points in the UNAIDS guidelines (hereinafter, UNAIDS). I argue that a comparison of these four points with statements in the three other documents reveals that UNAIDS calls for greater benefits to research participants and others in the community or country where the research is conducted.

The other three documents under comparison are the Declaration of Helsinki, as revised in 2000\(^1\) (hereinafter, ‘Helsinki’); the report of the U.S. National Bioethics Advisory Commission (NBAC)\(^2\), issued in 2001; and a current (2001) draft revision of the 1993 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects\(^3\) (hereinafter ‘CIOMS’). My argument seeks to demonstrate that the selected UNAIDS guidance points are at least as ethically sound as analogous points in these other documents, and for the most part are ethically superior. Nevertheless, they are subject to the criticism that they are too ‘aspirational’ and not sufficiently ‘pragmatic’.\(^4\)

But first, an acknowledgment is in order. I was one of a small group of individuals who worked on the UNAIDS guidance document from the outset. My views in this paper can, therefore, hardly be considered ‘objective,’ as I contributed to the process of developing the guidance document and ended up agreeing with virtually all of the guidance points. Nevertheless, my lack of objectivity does not distinguish the arguments in this paper from those of any authors who seek to defend substantive positions in ethics that they embrace and support.

The four guidance points to be compared with statements on similar issues in the other three documents are the following: Guidance Point (GP) 2, which deals with making available a safe and effective vaccine after trials are completed; the second half of GP 4, which requires that the desired outcome should potentially benefit the population from which research participants are

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drawn; GP 11, which discusses what should be provided to a control group in a vaccine trial; and GP 16, which addresses the care and treatment to be provided for trial participants who become infected with HIV during the trial.

UNAIDS GP 2 AND GP 4

The UNAIDS guidance document incorporates the same basic idea in two different guidance points. GP 2 states this idea precisely, and GP 4 expresses it more broadly. The general idea is that research must be responsive to the health needs of the population where the research is conducted and should potentially benefit that population. The latter statement is by now so widely accepted that few commentators see the need to argue for it explicitly. The precise form of this requirement is more controversial. GP 2 stipulates that successful vaccine products should be made available as soon as possible to all trial participants, as well as to other populations at high risk of HIV infection.

Earlier versions of the Declaration of Helsinki did not include any statement expressing even the more general requirement. The 2000 revision of Helsinki, however, addresses the point in two separate paragraphs. Paragraph 19 says: ‘Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research’. This general point is basically the same as the statement in the second half of GP 4 in the UNAIDS guidance document. However, the brevity of the items in the Declaration of Helsinki, and the absence of any commentary or explication, leaves crucial questions wide open. For example, what are the criteria by which ‘likelihood of benefit’ is to be determined? And what degree of likelihood is necessary?

Helsinki also addresses the question of benefits to the subject population in a strong requirement in paragraph 30: ‘At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.’ Thus, although Helsinki contains the same strong requirement as UNAIDS GP 2 with regard to what should be made available to research participants (‘Any HIV preventive vaccine demonstrated to be safe and effective should be made available as soon as possible to all participants in the trials in which it was tested’), Helsinki is silent on the question of what, if anything, must be made available to others in the country or community.
Unlike Helsinki, which consists of rather brief statements of its principles, the old and proposed new CIOMS guidelines include a commentary under each guideline. The current draft of the revised CIOMS document includes both the more general statement of responsiveness to the health needs of the population found in UNAIDS, and also the more explicit requirement that successful products be made ‘reasonably available’ to the population. Both points are included in Guideline 6:

‘Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any product developed will be made reasonably available to that population or community.’

So far, so good. CIOMS Guideline 6 is entitled ‘Research in populations and communities with limited resources,’ implying that its provisions apply specifically to countries or communities that fit this description. Whereas the guideline itself maintains a strong presumption of an obligation to make successful products of research available to the community or country where the research is conducted, the commentary that follows the guideline includes a loophole that could turn out to be rather large. The commentary says: ‘…exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun’. Now it is normally acceptable to call for a justification of a departure from a general ethical presumption, since few obligations are absolute or exceptionless. A document such as the CIOMS Guidelines, which contains detailed and lengthy commentaries, should include some criteria – even if roughly stated – that could count by way of a justification for departures from ethical requirements. To state simply that a justification should be ‘agreed to by all concerned parties’ is not sufficient. Since ‘all concerned parties’ will most likely be eager for the research to go forward, as they all have something to gain, it may be too easy to secure assent to any justification the researchers or sponsors might proffer. One likely justification is ‘we don’t know in advance how much a product that is proven successful will cost, so we can’t commit ourselves in advance to providing it to the entire population in the community or country where the research is conducted’. If this justification is considered adequate by ‘all concerned parties,’ it is evident that
the presumption to make successful products ‘reasonably available’ can be easily overridden.

Like UNAIDS, the NBAC report addresses two separate points regarding the availability of successful products after a trial is completed: availability to the research participants themselves (the only point addressed in the Declaration of Helsinki), and availability of successful products to others in the country or community. The first point is stated in NBAC’s Recommendation 4.1:

Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.

Whereas the Declaration of Helsinki stipulates that ‘every patient entered into the study should be assured of access…’, NBAC requires only ‘reasonable, good faith efforts’ on the part of researchers and sponsors, and permits the researcher to justify to the ethics review committee any failure to negotiate advance arrangements to make successful products available to participants who still need them at the end of the trial. Like CIOMS Guideline 6, NBAC Recommendation 4.1 provides no criteria for what would constitute a sound or acceptable justification for such failures. CIOMS and NBAC differ, however, regarding to whom the justification must be offered. In CIOMS, the justification must be agreed to by all concerned parties, which would normally include the sponsors of the research, the investigators from the industrialized and resource-poor country, relevant officials from the latter country, and possibly also representatives of the community. The inclusion of parties to this agreement from the resource-poor country makes the procedural requirement stronger in CIOMS than in NBAC, which requires only that researchers submitting a protocol to an ethics review committee provide the justification to the committee.

How many research ethics committees are accustomed to deliberating on this issue? Research ethics committees (IRBs) in the United States virtually never raise this question, even when
they review research conducted in domestic resource-poor communities, such as uninsured or under-insured populations.

Nothing in the US Code of Federal Regulations governing research with human subjects deals with this point, and most US IRBs see themselves as bound only by those regulations, along with any other US guidance or state regulations. So, as is the case for the ‘justification’ required by the CIOMS guidelines, the NBAC’s call for a justification to the research ethics committee will more than likely result in committees accepting whatever justification a researcher offers. Moreover, the justification need be provided only to the U.S. IRB. An ethical review committee in the host country would, of course, also have to approve the protocol, and could withhold approval unless the strong requirement in Helsinki’s paragraph 30 is fulfilled. If the successful product is an HIV/AIDS preventive vaccine, then the similarly strong provision in UNAIDS GP 2 would apply.

With regard to the second point – availability to others at the conclusion of a study – the NBAC report once again states a presumption (in Recommendation 4.2) in favor of making successful interventions available, in this case to the wider community or country:

Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making such interventions available. In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.

Here again, researchers are called upon to provide explanations and justifications to the ethics review committee. It is hardly conceivable that an ethics review committee in the United States will disapprove a research protocol on these grounds, however feeble may be the explanation or justification the researcher offers. One criticism that has been repeatedly leveled against a requirement that prior agreements be negotiated in advance of a study to make any resulting safe and effective products reasonably available is: ‘This has never been done (or
required) before’.\(^5\) That observation may well be true, but what is being called for now is a reform – not a continuation – of past practices in international research.

In contrast to the escape clauses in CIOMS and NBAC, and the omission of any such provision in Helsinki, the UNAIDS guidance document contains a strong and unequivocal requirement in GP 2: ‘Any HIV preventive vaccine demonstrated to be safe and effective . . . should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection’. It may be that this requirement is easier to fulfill in the case of HIV/AIDS preventive vaccines than with other potential products, since vaccines are generally less expensive than many therapeutic agents and what would be required is a one-time administration followed by boosters rather than, say, a lifetime of frequent administration of a pharmaceutical product. The commentary following GP 2 states that the discussion about making a successful vaccine available should begin before the trial commences, mentions the elements that should be included in the discussion, and indicates who should be the parties to the discussion. Unlike CIOMS and NBAC, the UNAIDS document does not retreat from its bold requirement by adding that it is permissible to depart from the provision as long as an acceptable justification is provided.

**UNAIDS GP11**

GP 11 addresses what is probably the most controversial point in ongoing discussions: the conditions under which it is ethically acceptable to use a placebo in the control arm of a clinical trial. The provision that has prompted a raging controversy\(^6\) is in Helsinki’s paragraph 29:


The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

In GP 11, UNAIDS allows for the use of placebo in a control arm under the same conditions as stipulated by Helsinki: ‘As long as there is no known effective HIV preventive vaccine…’ The commentary under this guidance point does allow for an exception to the requirement based on a scientific rationale for the use of placebo in the control arm even when a safe and effective HIV vaccine exists. However, this exception does not actually weaken the provision, since a flawed scientific design is ethically unacceptable in any case. The rationale specifies substantive criteria for permitting the exception, unlike the weaker NBAC recommendation, which contains a loophole permitting researchers to ‘justify’ departures without indicating what could count as an acceptable justification (see below).

CIOMS begins by citing and endorsing article 29 of Helsinki, but then goes on to weaken it with an escape clause. Guideline 7, entitled ‘Placebo-controlled studies,’ is as follows:

In biomedical research, ‘the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists’ (Declaration of Helsinki, Article 29). Any departure from this principle requires a sound scientific and ethical reason to use a control other than the best current method.

The key, then, is to determine what could count as a sound scientific and ethical reason. To its credit, the CIOMS commentary under its Guideline 7 goes part way toward providing a criterion. The commentary states: ‘There are two sound scientific and ethical reasons for departing from the principle regarding placebo controlled studies stated in the Declaration of Helsinki and repeated in this guideline: (1) withholding the best current treatment will result in only temporary discomfort and no serious adverse consequences; and (2) a comparative study of two treatments will yield no reliable scientific results’.

This exception would not seriously weaken the Helsinki requirement if the statement were to include the word ‘only’:
‘There are only two sound scientific and ethical reasons…’ The first reason essentially guarantees that temporary discomfort is the worst side effect permissible, and the second reason complies with the requirement that clinical trials must be scientifically sound in order to be ethically acceptable. Both conditions must obtain if the ‘best current’ method is withheld from participants in the control arm of a study.

But what the CIOMS commentary gains by stating these two conditions as the ones that may justify a departure from the Helsinki requirement, it loses in a later portion of the same commentary. In an escape clause directed specifically at developing countries, the commentary broadens the conditions that could justify a departure from the Helsinki provision by stipulating a procedural maneuver that opens the door to an unacceptably wide range of exceptions. The entire passage is as follows:

There are circumstances in which sponsors and researchers in technologically developed countries may propose to collaborate with counterparts in other countries to develop inexpensive alternatives to expensive therapies that are recognized as the ‘best current therapeutic method’. In some such cases it may be appropriate to compare the new inexpensive alternative with a locally available product rather than with the locally unavailable ‘best proven therapeutic method.’ Although there is no general agreement on this point, there are commentators who have concluded that in such circumstances use of a control other than the best current method is justified if: 1) the scientific and ethical review committees in both the country of the sponsoring institution and the host country determine that use of the best current method as a control would be likely to invalidate the results of the research or make the results inapplicable in the host country; 2) plans to make the therapeutic product reasonably available in the host country or community are securely established; and 3) a process of planning and negotiation, including justification of a study in regard to local health-care needs, has taken place with the health authorities in the host country before the research begins.

It is worth noting that although the CIOMS guideline under which this commentary appears is entitled ‘Placebo-controlled studies,’ the commentary that seeks to justify a departure from the Helsinki provision in order to develop ‘inexpensive alternatives’ uses an illustration in which a new inexpensive alternative is
compared with ‘a locally available product.’ We can only assume that the ‘locally available product’ is not ‘no treatment at all,’ which defenders of placebo-controlled trials in resource-poor countries have spuriously denominated a ‘standard of care.’ So the question arises whether this commentary under CIOMS Guideline 7, which in the main endorses the Helsinki requirement, ends up by carving out an exception that would invalidate the allowable use of placebo controls as stipulated by the two earlier ‘sound scientific and ethical reasons’ for departing from the strict Helsinki provision. The three additional reasons accepted by ‘some commentators’ are problematic.

The problem with (1) in the proposed justification is that there is no clear consensus on just which research design(s) would ‘invalidate the results of the research or make the results inapplicable in the host country.’ Critics of a research design that compared the short-course AZT regimen to reduce maternal-to-child transmission of HIV to the ‘best current’ 076 regimen used in the U.S. contended that such a design would be inapplicable in the host country.7 Yet that research design was used in a subsequent trial in Thailand and approved by the research ethics committee at the Harvard School of Public Health, whose members believed that the placebo-controlled design used in the now-infamous trials was unethical.8 So even experts in research methodology may disagree on which designs produce results that are meaningful and applicable in a given context.

Item (2) in the proposed justification is fine, but a plan to make successful products of research reasonably available is a requirement that appears elsewhere in the CIOMS guidelines, and is simply redundant in this place. The third requirement – a process of planning, negotiation, and justification with authorities in the host country – is a procedural solution that may or may not result in an ethically sound decision. More about this point later, in connection with the charge of ‘unjustified paternalism.’

What does the NBAC report say on this matter? As in virtually all of the provisions discussed in the four documents under comparison, NBAC’s position is the weakest in securing benefits


for trial participants in the developing country. Here is what Recommendation 2.2 says:

Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.

Unlike the CIOMS provision, which offers substantive criteria that an ethics review committee could use if it intends to depart from the strict requirement in the Declaration of Helsinki (the ‘two sound scientific and ethical reasons’), NBAC simply leaves the matter up to the committee without providing criteria that would make the departure acceptable. As noted above regarding NBAC’s position on making successful products of research available to participants and others, this NBAC recommendation also places undue reliance on the role of ethics review committees. It may be the case that committees in developing countries, whether they are experienced or newly established, will pay more attention to matters that have largely been ignored by review committees in industrialized countries. But if a study to be carried out in a developing country is approved by the ethics review committee in the sponsoring country, there is likely to be great pressure on the committee in the developing country to accept whatever justification the researchers provide for departures from the Helsinki requirement.

UNAIDS GP 16

This provision in the UNAIDS guidance document could be considered unique to research on preventive vaccine trials. For one thing, GP 16 refers to a specific disease, one that may be acquired by trial participants in a special kind of study – a preventive vaccine trial. Since a vaccine trial begins with healthy subjects, this guidance point addresses the unique circumstance in which research subjects acquire HIV/AIDS during the course of a trial on a product aimed at preventing that very disease. It is understandable that the other three documents lack a provision addressing the precise point of UNAIDS GP 16.
Clinical trials on therapeutic agents may nevertheless still give rise to the question of what should be provided to research subjects who already have or newly acquire a disease different from the one under study. Thus a broader reading of this provision could refer generally to care and treatment for, say, malaria when tuberculosis is being studied in the research. Helsinki has no provision that deals with this more general situation, explicitly or implicitly.

The CIOMS draft does address this broader context in Guideline 23, entitled ‘Obligations of external sponsors to provide health-care services:’

When necessary for the conduct of the research, sponsors should provide facilities and personnel to make health-care services available to the population from which research subjects are recruited. Consideration should be given to whether the sponsoring agency should agree to maintain in the host country, after the research has been completed, health services and facilities established for purposes of the study.

This guideline is supplemented by the following commentary:

Although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy… [S]ponsors and researchers 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 to seek medical care if they are rejected as research subjects because they do not meet health criteria for admission to the investigation.

UNAIDS is more detailed in its specification of what should be included in a healthcare package to participants who become HIV infected during a vaccine trial. GP 16 falls short of stating an ‘ethical obligation,’ yet unlike the CIOMS commentary, it does not retreat into a denial that an ethical obligation exists. The NBAC recommendations do not appear to address this question at all.

‘WHO SHOULD DECIDE?’ AND THE CHARGE OF PATERNALISM

One vexing problem remains. A procedural question that arises in every area of concern in bioethics where decisions have to be
taken is ‘Who should decide?’ In the clinical setting, this question has by now been answered overwhelmingly in favor of respecting the decisional authority of patients. In the case of policy guidelines, however, there may be tension between what international ethical guidelines prescribe, on the one hand, and the claim to decisional authority on the part of various concerned parties, on the other hand.

This issue may become problematic when an industrialized country or an international agency such as WHO or UNAIDS sponsors or conducts research in a developing country. An ethics review committee in the sponsoring country or agency might demand adherence to the Helsinki requirement that the control group receive the best current treatment, whereas the Ministry of Health officials in the resource-poor country could be content with a placebo control, on the grounds that the ‘best current treatment’ is not otherwise available to individuals not in the trial so there is no need to provide it to trial participants. Ministry of Health officials might then accuse the outside sponsor of seeking to impose its paternalistic will on the developing country. Officials in a resource-poor country could very likely argue that they know what is best for their country, and paternalistic requirements are unwarranted, even if the sponsors seek to justify them by reference to international ethical guidelines. Indeed, such claims have in fact been made by some who defended the placebo-controlled AZT maternal-to-child HIV transmission trials.\(^9\)

There is no easy way out of this dilemma. A full analysis of this vexing question is beyond the scope of this article. Yet it is worth noting that one function of international ethical guidelines is to ensure that research employs a single set of ethical standards wherever the research is carried out, not one standard for rich countries and another for poor nations. Yet even the call for a single, global ethical standard for research has been questioned and criticized.\(^10\) Since a research protocol for an international collaborative study must be approved by ethics review committees in both countries, it is commonly held that the research may not go forward until any differences between the committees are resolved. Although this requirement is generally sound, it may

\(^9\) E.K. Mbidde. 1997. Letter to NIH. Dr. Mbidde’s letter, dated May 8, 1997, was sent to Dr. Harold Varmus, then Director of the NIH, in response to the Public Citizen News Release of April 22, 1997. Public Citizen faxed copies of Dr. Mbidde’s letter to individuals on their mailing list.

ignore the political reality that external pressure can be exerted on such committees wherever they exist.

My own view is that the requirements in international ethical guidelines should be taken seriously and adhered to, even if some provisions may appear to be too ‘ideal’ when applied to the current economic situation of resource-poor countries. While ethics should not be hopelessly ‘aspirational,’ it always deals with what ‘ought to be the case’ rather than ‘what is, in fact, the case.’ The four guidance points in the UNAIDS guidance document discussed in this article are superior to the analogous provisions in CIOMS, NBAC, and Helsinki (except for the famous paragraph 29) in striving to provide greater benefits to research participants and others in developing countries.

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