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Joan Claybrook, President

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Dear Dr. Human:

We are writing to express alarm at the current draft revised version of the Declaration of Helsinki, which has been sent to at least some of the World Medical Association's member associations in advance of the WMA's Council Session in Santiago, Chile on April 15, 1999. Apparently reacting to the fact that perinatal HIV transmission trials, in which drugs of known efficacy were withheld from HIV-positive pregnant women, were in clear violation of the current version of the Declaration, researchers have reacted by seeking to change the ethics rules to comply with the scientific studies they wish to conduct, rather than revising their studies to be ethical. It's the old story: write the rules, break the rules, get caught, change the rules. If the Declaration is to have any credibility in the future, particularly as a protector of the rights of subjects in developing countries, the document will have to be drastically reworked to remove any potential for double standards in research.

The proposed Declaration is one of several ongoing attempts to greatly undermine existing human subjects protections, particularly as they relate to the rights of participants from developing countries. Similar retreats from ethical principles are embodied in a recently published "consensus statement" on perinatal HIV research[1] and draft guidelines on HIV vaccine trials from the United Nations Programme on HIV/AIDS.[2] The Council for International Organizations of Medical Sciences (CIOMS) ethics document is also being rewritten. Thus, as dismayed as we are by this product, we are not surprised.

The proposed Declaration is stunningly complacent. There seems to be no recognition of recent abuses in international research (e.g., Dr. Henry Heimlich's injection on live malaria into HIV-positive persons in China after the study was opposed in the United States[3]), the well-documented failings of Institutional Review Boards (IRBs),[4] studies with an industrial solvent on healthy and HIV-positive persons in South Africa without the approval of that country's Medicines Control Council,[5] the growth of for-profit IRBs accountable to no government or

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academic institution,[4] failures to obtain adequate informed consent in developing country studies,[6] and exploitative recruiting practices by for-profit multinational recruiting companies. Of all this, the Declaration has little or nothing to say. Opening the door to relatively unfettered international research, even unethical research, seems to be its primary agenda.

Our primary objections to this proposed Declaration are: 1. The document enshrines a double standard in research under which investigators are not required to provide their participants with any intervention that would not otherwise be available to them. The primary losers will be developing country residents (or at least poor developing country residents) who will receive medical care in human experiments that fails to meet currently accepted standards for rich people in the same country or in industrialized countries, even when an industrialized country or wealthy pharmaceutical company is a sponsor. In many cases, this will mean receiving nothing at all, even when inexpensive, cost-effective interventions are available. 2. The proposed Declaration greatly extends the use of placebos, even when known effective interventions exist, as long as the condition under study does not lead to "death or disability." This change will have adverse effects on the health of study participants in both developing and industrialized countries.

We have attached a table that presents a comparison between the current (October 1996) Declaration and the proposed one. We have only included the changes that would undermine human subject protections. (There are some changes that improve upon the current document, but their significance pales in comparison to the adverse changes.) Below we address the most important of these changes.

Journal refusal to publish (Section I.8 of current Declaration)

The protection of human participants is the joint responsibility of numerous groups: the investigators who design and conduct the study, IRBs who review the study before it is conducted, medical journals who are bound by the current Declaration not to publish unethical research and, before or after publication, oversight by relevant governmental bodies, associations, patient groups and other scientists. This proposal would remove one of the more powerful sticks against conducting unethical research: the possibility that one's research, the yardstick for academic advancement, would not be published. Certainly, reasonable people can disagree about whether a study is unethical, but as currently written the proposed Declaration provides far too great a license for the publication of unethical research by simply requiring editors to "consider carefully the justification for any variances [from the Declaration of Helsinki]."

Informed consent (Sections I.9 - I.11 and II. 5 of current Declaration)

The principle of informed consent was the first and in many ways the landmark principle enunciated in the Nuremberg Code. It has been adopted and generally expanded in all of the major subsequent codes, including the current Declaration of Helsinki, the Belmont Report in the

United States, the CIOMS Report and ethical regulations in many countries. The proposed Declaration, by creating a set of glaring loopholes in the informed consent requirements, is the first significant step backward in the evolution of informed consent guidelines. The momentum for scuttling informed consent in some circumstances is growing.[7] The Declaration should, at a minimum, prevent any scaling back of this vital human subjects protection.

The proposed Declaration permits waivers of written informed consent when the research involves only "slight risk." The definition of "slight risk" is, of course, very much in the eye of the beholder or, in this case, the investigator. But, as any patient who has been assured that "this will only hurt a little bit" knows, physicians frequently underestimate the discomforts and risks to patients.

The proposed Declaration would also permit waiving written informed consent when the procedures "are customarily used in the practice of medicine without documentation of consent." This seems to miss the point that research is inherently different from clinical practice and that particular protections are needed for study participants that are not required in clinical practice. This is why the Declaration was conceived in the first place. The purpose of written informed consent is to give some, however small, degree of assurance that an informed consent process has been followed. Sometimes informed consent not documented will mean informed consent not given. In the absence of documentation, there will be no way to distinguish between this circumstance from properly conducted, but undocumented, informed consent. For the researcher truly interested in obtaining informed consent, asking the participant to sign his or her name is a minuscule effort. On the other hand, waiving written informed consent for participants with special reasons to maintain confidentiality (e.g., participation in illegal activities) seems reasonable.

The proposed Declaration goes beyond permitting informed consent to not be documented in some cases to creating whole new, ill-defined categories where informed consent can be waived entirely. This category includes "certain other types of research in such fields as epidemiology and policy evaluation." But clinical trials are a particular kind of epidemiological study and the list of clinical trials that have justifiably evoked ethical controversy is too lengthy to recite here. The same is true for prospective studies and cross-sectional studies. In a study in India, for example, women with precancerous lesions on Pap smear were followed prospectively without treatment. Sixty-two developed cancer, including nine with metastases.[8] In addition, some policy evaluations involve interviewing patients or following them prospectively. Exempting anonymous tissue samples or secondary data analyses from which patient identifiers have been removed is reasonable. This huge loophole is not.

The proposed Declaration also follows recent U.S. Food and Drug Administrarion regulations in permitting research without informed consent in certain emergency situations. We are concerned that these U.S. requirements do not adequately require investigators to exhaust the options for obtaining surrogate informed consent. This is an enormously complex matter that will arise only infrequently and not one to be dealt with in five lines in ethical guidelines.

It is unavoidable that at times an investigator will enroll his or her own patients in clinical trials. The present Declaration properly requires that in such circumstances a person who is "completely independent" of this relationship obtain informed consent. But the proposed Declaration waters down this requirement by stating that this "may be preferable" in "some cases of this type." This will make it more difficult for patients to decline participation in research studies in which their own physician is involved.

Access to health care (Section II.3 of current Declaration)

The most insidious assault on the rights of participants in research appears in the section entitled "Access to Health Care," which should rightly be renamed "Access to Health Care for the Rich." In a single turn of phrase, the proposed document would reverse a medical principle dating back to at least the Hippocratic Oath, in which physicians undertake to "look upon [God's] offspring in the same footing as my own brothers." Apparently the notion of brotherhood envisioned by the proposed Declaration extends only as far the line separating rich from poor.

Whereas the current Declaration assures research participants of "the best proven diagnostic and therapeutic method," the corresponding section in the proposed Declaration adds the phrase "that would otherwise be available to him or her," condemning most residents in developing countries to potentially receiving second-rate medical care when they participate in experiments. The term "standard of care" has been used to justify this practice, but as scientists and persons interested in ethics we should shy away from developing ethical standards based on terms that have no scientific meaning but are instead reflective of economic concerns. From a scientific perspective, there are only two kinds of medicines: those that have been proved to work and those that haven't.[9] The current Declaration assures all patients of the former, while the proposed Declaration will consign some patients (specifically poor patients) to the latter. This is not "standard of care"; it is substandard care and, at times, no care at all.

Let us consider some examples. For years it has been known that treatment with at least some antihypertensive medications can reduce mortality. Yet between 1987 and 1990, Bayer-funded researchers in China compared the efficacy of nifedipine to placebo in 1600 patients.[10] The result was 45 more cardiovascular events in the untreated group (77 in the placebo group vs. 32 in the nifedipine group). Such a study would (we hope) never be countenanced in an industrialized country. Is this the new face of medical research?

More recently this "standard of care" argument has been used to justify the withholding of optimal antiretroviral therapies from at least some patients who contract HIV infection during a clinical trial of an AIDS vaccine in Thailand, even though the investigators will continue to follow these participants prospectively.[11] Similarly, even though five placebo-controlled clinical trials have proved the effectiveness of antiretroviral therapies in reducing perinatal HIV transmission,[12,13,14,15,16] two US government-funded studies plan to deny HIV-positive pregnant women access to even the less expensive regimens.[17,18]

Furthermore, if the logic of this section is to be followed, it will only be a matter of time before it is applied to poor residents in developed countries as well. Particularly in countries like the United States, which does not have universal health coverage, it is inevitable that this principle will ultimately be used to deny uninsured or underinsured persons access to medical care in human experiments. Already we have seen studies in which opiate users are randomized to placebo instead of active therapy,[19] presumably because, due to the drastic underfunding of drug treatment, "they wouldn't have gotten it anyway," as many researchers argued in the perinatal HIV transmission case. But in many cases, the research will be conducted by multimillion dollar research teams to whom any added expense would be minimal. As noted historian of science David Rothman has pointed out: "As soon as [researchers] attempt to take advantage of the social predicament in which the subjects are found, they become accomplices to the problem, not observers of it. For usually the investigators have the ability to alter the social deprivation of their particular subjects."[20] If in research we choose not to rectify those health conditions that we can, particularly those related to the outcome of interest, we are turning our backs on our responsibilities as physicians.

Use of placebo (Section II.3 of current Declaration)

The proposed Declaration would also greatly expand the use of placebos in clinical trials. Specifically, the draft Declaration would permit the use of placebos (and the denial of proven effective therapy) in any circumstance where "the outcome measures are neither death nor disability." This ignores large numbers of conditions where suffering and discomfort, but not death or disability, occur. The term disability remains undefined, risking its being used in an underinclusive manner. Presumably, placebo use in the studies of opiate users we have mentioned above would be acceptable under this standard, as would the over one dozen placebo-controlled trials of treatments for recurrent genital herpes that have occurred since the first placebo-controlled studies demonstrated the remarkable effectiveness of acyclovir for this condition in 1984.[21,22] The "death or disability" standard also invites the defining of surrogate markers (which may not themselves be directly associated with disability) as the outcome of interest, justifying the withholding of effective therapy. One example would be studying CD4 cell counts or viral load levels as the primary outcome measure in studies of treatments for HIV disease and not providing antiretroviral treatment.

We appreciate the attempt to differentiate between placebo use in studies of mild conditions (e.g., headache) and the use of placebos in more serious conditions. But the relevant concept here is not whether the outcome is death or disability, but rather the probability of particular adverse outcomes actually occurring. Very short studies of antihypertensive medications (e.g., one week) in mild hypertensives might use placebos to measure blood-pressure lowering, because the incidence of adverse events in this population in this time period is extremely low. But longer studies, like the one previously described in China (average follow-up: 2.5 years), should be clearly precluded by any ethics document.

The draft Declaration also proposes that placebo-controlled trials "may be justified on the basis of their efficiency." This appears to be a reference to the notion that the speed of completing a clinical trial is related to the sample size required. But sample size requirements for active-control trials are very often similar to (and can even exceed) those needed for placebo-controlled ones.[23] For the specific case of the perinatal HIV trials, we have previously demonstrated that the sample size required for an "equivalency" study, in which short courses of zidovudine are compared to the standard, longer zidovudine regimen, requires 620 subjects compared to 500 subjects for a placebo-controlled trial,[24] an insignificant difference. In any event, aggressive recruiting and multicenter studies can readily compensate for these small differences.

The vagaries of health policy making are such that minor differences in sample size requirements and hence date of trial completion have an insignificant impact upon actual delivery of services. This is best illustrated in South Africa, where the strikingly positive results of the PETRA perinatal HIV transmission trial to which South Africa contributed 52% of the subjects[14] have failed to convince the national government to fund even a pilot program using zidovudine, even though the drug reduced perinatal HIV transmission by up to 50% compared to placebo in that study.[25] For these reasons, economic concepts such as efficiency have no place in ethics documents.

Issues omitted from the proposed Declaration

It is extremely disturbing that at the same time as economic concerns are injected into the proposed Declaration in ways that encourage second-rate medical care in some circumstances, the very real impact of class is ignored in other areas of the document. For example, Section 27 of the proposed Declaration is a welcome improvement on the previous version in that it lists groups of vulnerable participants (e.g., children, prisoners, those in hierarchical organizations, those not familiar with Western concepts of disease causation). But it omits other important classes of potential participants such as those engaging in illegal activities (e.g., drug injectors, sex workers) and, particularly, poor persons. These groups certainly need the "special protection of their rights and welfare" envisioned in this Section.

It is alarming, too, that the Declaration still contains no clear statement about the need for post-trial availability of any intervention proved to be effective. We acknowledge that some elements of availability are difficult to define (e.g., To whom? At what price? For how long?), but to simply omit this critical concept is to invite violations of the ethical principle of justice enunciated in the Belmont Report, which requires that research "not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research."[26] The CIOMS guideline is also quite clear on this: "As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing."[27] The absence of such language in the current Declaration is a serious problem. Now is the time to correct it. Otherwise, situations like that following the PETRA trial[14] will continue.

Conclusion

What this proposed Declaration is really saying is that it is acceptable to commit malpractice in a clinical trial. According to the proposed Declaration, withholding known effective therapy may be acceptable even in industrialized country studies, even though the same physician would treat the patient for that condition outside the context of a clinical trial and could be sued for malpractice if he or she didn't, as long as it is decided that the condition does not cause death or disability. In addition, a physician who would provide life-saving therapies such as antihypertensive drugs, antiretrovirals or antituberculosis prevention in an industrialized country, can withhold them in a clinical trial as long as the study participants are poor, regardless of how easy it would be to provide the intervention. The notion that well-funded researchers could actually provide inferior medical care compared to what they would provide in their clinical practices is abhorrent.

Implicit in the proposed Declaration is the notion that current ethical standards are somehow an impediment to the advancement of science. Since there is no evidence to support this notion, we reject it. Rather, we argue that the proposed Declaration is one that runs against the latest trends in scientific research. Even as there are increasingly few conditions for which there are no treatments, and medical professionals and payers increasingly recognize the usefulness of studies comparing therapies to one another rather than to nothing, the proposed Declaration attempts to widen the range of studies in which placebos would be acceptable. And even as research is increasingly globalized, bringing with it the need for improved protections for the increasingly vulnerable participants who will be enrolled in future studies, the proposed Declaration actually clearly endorses weakened standards and double-standards in medical care. Any association that was truly a *world* medical association would reject such a Declaration.

Yours sincerely,

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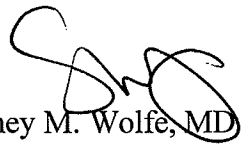

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Director

Subject	Current Declaration Text	Draft Revised Declaration Text
Journal refusal to publish	Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication. (Section I.8)	*Variances from these principles should be explained and justified in the report. Editors are obligated to consider carefully the justification for any variances from these principles in deciding whether to accept or reject the report for publication.* (Section 34)
Waiver of written informed consent	The physician should then obtain the subject's freely-given informed consent, preferably in writing. (Section I.9)	*The requirement for written documentation may be waived by the research ethics committee in certain circumstances such as when the research involves only slight risk, when the procedures to be used are customarily used in the practice of medicine without documentation of consent*, or when a signed informed consent document would create an unwarranted risk of a breach of the subject's confidentiality. (Section 24)
Obtaining informed consent from persons who have a dependent relationship to the investigator	In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship. (Section I.10)	*In some cases of this type, it may be preferable if the informed consent were to be obtained by a qualified person who is not engaged in the investigation, independent of the dependent relationship, or both.* (Section 23)

Subject	Current Declaration Text	Draft Revised Declaration Text
Research involving vulnerable subjects		Groups of vulnerable persons include but are not limited to those who are legally incompetent by virtue of their status (e.g., children) or individual condition (e.g., cognitive impairment by mental disease); those who lack the capacity to comprehend (e.g., persons for whom Western concepts of disease causation are unknown); and those with limited freedom to exercise free power of choice (e.g., institutionalized or incarcerated persons and junior or subordinate members of hierarchical groups). (Section 27) Comment: *List omits persons of low socioeconomic status and those engaging in illegal activities.*
Subjects who are incapable of valid consent	Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. (Section I.11)	For prospective subjects who are incapable of valid consent but not adjudicated incompetent, investigators may rely on the permission of a responsible relative or other appropriate person to the extent allowed by applicable law and approved by the research ethics committee. *Persons who are partially capable of valid consent should generally be invited to assent to the extent of their capability; such assent should generally be supplemented with the permission of the responsible relative or other appropriate person.* (Section 28)
Use of new diagnostic and therapeutic measures	In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or here judgement it offers hope of saving life, reestablishing health or alleviating suffering. (Section II.1)	In the treatment of a sick person *with a progressive, disabling or potentially fatal disease for whom existing therapy is either not effective or not available,* the physician should be free to *recommend use of* a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering. (Section 7)

Subject	Current Declaration Text	Draft Revised Declaration Text
Access to health care	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. (Section II.3)	In any biomedical research protocol every patient-subject, including those of a control group, if any, should be assured *that he or she will not be denied access to* the best proven diagnostic, prophylactic or therapeutic method *that would otherwise be available to him or her.* (Section 18)
Use of placebo	This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists. (Section II.3)	This principle does not exclude the use of placebo or no-treatment control groups *if such are justified by a scientifically and ethically sound research protocol.* (Section 18)
Controlled clinical trials		*When the outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency.* (Section 19)

Subject	Current Declaration Text	Draft Revised Declaration Text
Waiver of consent	If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee. (Section II.5)	When permitted by applicable law, the requirement for informed consent may be waived by the independent research ethics committee. Such *waiver may be appropriate in research that presents little or no threat to the rights and welfare of research subjects as exemplified by use of anonymous tissue samples for research purposes and in certain other types of research in such fields as epidemiology and policy evaluation. It may also be justified in research in emergency situations in which patient-subjects have temporary or enduring loss of decisional capacity and interventions or procedures must be initiated before informed consent can be obtained from patient-subjects or their legally authorized representatives.* In the latter case the research ethics committee may require special procedures to protect the rights and welfare of the research subjects. (Section 25)

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