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World Medical Association
Working Group on the Declaration of Helsinki
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To the World Medical Association Working Group on the Declaration of Helsinki:

Public Citizen, a consumer advocacy organization based in the U.S. with more than 300,000 members and supporters, submits these comments on the draft revision of the Declaration of Helsinki. In general, we commend the working group on its efforts to improve readability. We support provisions requiring adequate compensation to subjects who are harmed as a result of participating in clinical research and consideration of benefits for the communities where research is carried out. We also support provisions for post-trial access for research participants, efforts to strengthen the wording of various paragraphs, requirement that risks be minimized for participants throughout the trial, and clarifications regarding denial of best proven intervention in a clinical trial. However, we recommend some changes to these proposed amendments, intended to help clarify and strengthen their effect.

Our greatest concern with the revisions is with one of the annotated comments to the revision proposal, which suggests that one important statement — "the well-being of the individual research subject must take precedence over all other interests" — is "intended to be aspirational" and therefore need not be reconciled with the remaining provisions in the document.[1] Such a comment undermines both the value of this specific provision and the force of the entire document as a guide for physicians engaged in medical research.

Our specific recommended edits are outlined below.

[1] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Draft revised text for public consultation, annotated version. April 15, 2013. http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/DoH-draft-for-public-consultation_annotated.pdf. Accessed June 11, 2013.

I. Specific Comments

Public Citizen commends the working group for adding several important amendments to this draft of the Declaration of Helsinki. These modifications generally strengthen the document by helping to ensure conformity with the principles of respect for persons, beneficence, and justice that form the foundation of medical research ethics in the U.S. and other countries.[2]

We generally support, with some suggestions, the amendments designed to improve organization and readability, as well as the following proposed amendments:

Proposed paragraph 10: Local ethical, legal, and regulatory norms

We support efforts to strengthen the requirement that physicians consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries, as well as applicable international norms and standards, by replacing the word "should" with "must" in paragraph 10. However, we are concerned that this change notwithstanding, the language could be read to justify reducing or eliminating international norms or standards in favor of less protective local standards, or vice versa. For this reason, we would support clarifying the language of this paragraph as follows (working group proposed additions are in **bold,** removed language in ~~strikethrough~~, whereas Public Citizen's additional proposed edits are also **underlined)**:

> Physicians ~~should~~ **must** consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards**, including those set forth in this Declaration**. ~~No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.~~ **In considering applicable local and international standards, physicians must apply the standard that affords the highest protection for research subjects.**

Proposed paragraph 15: Compensation to research subjects

We support the proposed revision designed to encourage justice in the conduct of clinical research by requiring adequate compensation to subjects injured as a result of participation in research. While subjects injured during clinical research often have recourse to local medical malpractice or tort law to secure compensation, it is important to acknowledge that compensation also is required as a matter of medical research ethics. Moreover, clinical trials recruiting in developing countries may enroll vulnerable subjects who lack access to effective local judicial

[2] The Belmont Report. Office of the Secretary, United States Department of Health, Education, and Welfare. Ethical Principles and Guidelines for the Protection of Subjects of Research. April 18, 1979. http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed May 29, 2013.

process, making it necessary for researchers to make additional provision for compensation above what may be available to research subjects under local law.

Proposed paragraph 17: Measures to minimize risk

We strongly support the proposed amendment recognizing the ethical obligation to implement measures to minimize risks and to monitor risks throughout the trial. This addition is in keeping with the ethical principle of beneficence, which includes an obligation to minimize risks and maximize possible benefits to research subjects. Such a clarification is long overdue, considering that the current version of the document allows a trial to proceed as long as the "potential benefits" outweigh the risks and risks can be "satisfactorily managed."[3] This language may falsely suggest that researchers are under no obligation to eliminate excess risk, provided they have concluded that the overall risk of the study is outweighed by the potential benefits of the trial and risks have been "satisfactorily managed."

Proposed paragraph 19: Protecting vulnerable subject populations

We strongly support provisions intended to ensure that vulnerable subject populations are adequately protected. However, the meaning of "specifically considered protection" is unclear. All subjects need specifically considered protection. We believe that "special protections" is a more appropriate term. We therefore urge the following modification of the amendment:

All vulnerable groups need ~~specifically considered~~ special protections.

Proposed paragraph 20: Benefits to disadvantaged or vulnerable populations or communities

We approve of some of the proposed language in paragraph 20 and recommend strengthening certain other parts. However, we are concerned that one of the proposed amendments to paragraph 20 introduces ambiguities that would make this paragraph difficult to interpret or evaluate. We strongly agree that in cases of a disadvantaged or vulnerable population, research must be responsive to the health needs and priorities of this population or community. We also support the statement that the population must stand to benefit from the knowledge, practices, or interventions that result from the research, as well as the new amendment requiring that such research not be carried out unless it is impossible to perform in a nonvulnerable population. These statements work to ensure that researchers will not take advantage of vulnerable populations to perform research that can be of little or no benefit to subjects – for example, by conducting Phase I clinical trials in resource-poor settings in order to easily recruit healthy subjects in exchange for financial compensation.

[3] World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. October 2008. Paragraph 20. http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed June 12, 2013.

We also believe that the language in paragraph 20 should be strengthened to reflect the mandatory nature of this requirement:

> . . . **In addition,** ~~and if there is a reasonable likelihood that~~ this population or community ~~should~~ **must** stand~~s~~ to benefit from the **knowledge, practices or interventions that result from the** ~~results of the~~ research.

However, we are concerned that the new discussion of "additional benefits" at the end of paragraph 20 introduces ambiguities that make this statement difficult to interpret or evaluate. "Additional benefits" to the community could mean the types of benefits inherent to the research – such as the benefits from knowledge, practices, or interventions that result. However, "additional benefits" may also mean offering financial or other compensation to individuals or organizations in the community, for example, by offering to pay the salaries of physicians in the area, build a new hospital center, or provide funding for medication outside the trial. Such compensation, while valuable, can result in potential conflicts of interest between organizations receiving the benefit and the research subjects themselves. Excessive payments to local organizations should not be used to secure local cooperation in questionable research efforts. For this reason, we hope that the working group will clarify the proposed amendments to ensure that "additional benefits" are not used to unduly influence community decisions to cooperate in a research effort.

Proposed paragraph 22: Clear description of study design in the protocol

We believe the requirements of paragraph 22 are ethically mandatory, in that a research protocol *must* discuss and justify the study design; *must* contain a statement of the ethical considerations involved; *must* indicate how the principles in the Declaration of Helsinki have been addressed (although specific reference to the Declaration itself is not required); and *must* include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects, and provisions for treating and/or compensating subjects who are harmed as a consequence of study participation. Each of these disclosures is essential to allow the appropriate ethics committee to make informed decisions to protect subjects enrolled in the trial.

Proposed paragraph 30: Informed consent for incapacitated subjects

We believe that the language of paragraph 30 should be strengthened to reflect that the exception stated in the paragraph is the *only* exception to the mandatory requirement of informed consent for incapacitated subjects. If a physician has determined under paragraph 30 that a potential subject is physically or mentally incapable of giving consent (e.g., because he or she is unconscious), that physician *must* seek informed consent from a legally authorized representative, except in rare circumstances that have been expressly described as an exception. We support language that requires approval by a research ethics committee and the seeking of

consent from a legally authorized representative "as soon as possible," and we urge the committee to strengthen this language. Paragraph 30 should therefore be revised to read:

> Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician ~~should~~ **must** seek informed consent from the legally authorized representative~~.~~**; except that i**~~I~~f no such representative is available, and if the research cannot be delayed, the study may proceed without informed consent**.** **In such cases,** ~~provided that~~ the specific reasons for involving subjects with a condition that renders them unable to give informed consent **must** ~~have~~ be~~en~~ stated in the research protocol and the study **must** ~~has~~ be~~en~~ approved by a research ethics committee. Consent to remain in the research ~~should~~ **must** be obtained as soon as possible from the subject or a legally authorized representative.

Proposed paragraph 33: Use of placebo

The proposed draft clarifies the current document by adding that denial of best proven treatment is unethical regardless of whether subjects receive inert placebo, "pseudo placebo" (an active ingredient that is less effective than the best proven one), or no treatment. Obviously a trial involving no treatment where a proven treatment option is available is just as unethical as a trial involving inert placebo. Likewise, a trial involving a substandard active ingredient can also create unethical risks for research subjects.

However, we believe that the proposed language does not fully capture all of the ways best proven treatment may be unethically denied. For example, in a trial assessing the safety of a new intervention, researchers may unethically choose to offer a substandard treatment to the control group that is less safe than the best proven treatment, although it may or may not be demonstrated to be less effective. Arguably, such treatment is even more unethical than no treatment or placebo, because risks for subjects in the control group may actually be higher than if they had received no treatment at all. For example, a trial offering hormone replacement therapy to prevent osteoporotic fracture would be unethical because this treatment, while effective in reducing fracture risks, is known to significantly increase risk of breast cancer, stroke, and thromboembolic events.[4] It would be unethical for researchers to design a trial today offering hormone replacement therapy to a control group to prevent fracture, because this therapy is less safe than available alternatives. Therefore, we recommend the following amendment to proposed paragraph 33:

[4] Management of osteoporosis in postmenopausal women: Statement of the North American Menopause Society. *Menopause* 2010;17(1):25-54.

> . . . Where for compelling and scientifically sound methodological reasons the use of **any intervention less effective or less safe than the best proven one,** placebo or **no treatment** is necessary to determine the efficacy or safety of an intervention
>
> and the patients who receive **any intervention less effective or less safe than the best proven one,** placebo or no treatment will not be subject to ~~any~~ **additional** risk**s** of serious or irreversible harm **as a result of not receiving the best proven intervention**.
>
> Extreme care must be taken to avoid abuse of this option.

Finally, we remain concerned that the exception allowing for any intervention less effective than the best proven one, placebo, or no treatment is open to broad abuse, particularly if researchers ignore or misinterpret the requirement that such use is authorized *only* where it will not expose subjects to additional risk of serious or irreversible harm. To assist readers in considering the language of this exception in its entirety, we suggest that the three paragraphs describing this exception be joined into one, as follows:

> . . . Where for compelling and scientifically sound methodological reasons the use of **any intervention less effective or less safe than the best proven one,** placebo or **no treatment** is necessary to determine the efficacy or safety of an intervention and the patients who receive **any intervention less effective or less safe than the best proven one,** placebo or no treatment will not be subject to ~~any~~ **additional** risk**s** of serious or irreversible harm **as a result of not receiving the best proven intervention**. Extreme care must be taken to avoid abuse of this option.

Although we do not feel that this proposed amendment will fully address the risk of abuse, we do not have other recommendations at this time for better alternative language.

Proposed paragraph 34: Post-trial access by research participants

We also generally endorse the new language designed to ensure post-trial access for all participants who still need an intervention identified as beneficial in the study, as well as to inform study participants of their right to access beneficial interventions and to learn about the outcome of the study. This provision furthers the ethical principles of justice by ensuring that research subjects have an opportunity to reap the benefits of the study after voluntarily subjecting themselves to the risks of clinical research, and it is particularly important for subjects in resource-poor settings, who may not otherwise have access to care. It also accords with the principles of respect for persons and beneficence by ensuring adequate informed consent and maximizing the possible benefits of participation.

We particularly commend the working group for suggesting that provisions for post-trial access be considered in advance of the clinical trial. In general, all of the provisions of the Declaration of Helsinki should be considered in advance of the trial and incorporated into the trial protocol.

However, we believe there is a particularly high risk that researchers may choose to defer decisions regarding post-trial access until the results of the trial are known. This increases the chances that post-trial access will be ignored and also undermines the informed consent process. Therefore, we support the language in paragraph 34, which complements the requirement of paragraph 22 that the protocol describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study. However, we believe that this provision should be strengthened to state that post-trial access *must* be provided for in the trial protocol, as follows:

> **In advance of a clinical trial, sponsors, researchers and host country governments ~~should~~ must make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the study....**

Comments to proposed paragraph 8

In addition to our comments on the actual text of the proposed revision, we are concerned that the annotated comments to the revision proposal weaken the entire document by suggesting that one important statement — "the well-being of the individual research subject must take precedence over all other interests" — is inconsistent with other portions of the document and "intended to be aspirational."[5] First, by stating that paragraph 8 is "intended to be aspirational," these comments render a mandatory obligation ("*must* take precedence") into an optional requirement, thereby encouraging medical professionals to disregard this paragraph. Second, by stating that such mandatory language is "aspirational," the committee suggests that similar mandatory language throughout the document also is intended to be aspirational. This comment thus undermines other proposed amendments intended to strengthen the provisions in the remainder of the document. The World Medical Association, representing physicians worldwide, has an obligation to physicians and to the subjects of human research to develop a consistent approach that will serve as a workable guide to physician researchers. Rather than address inconsistencies within the document by stating that one or more provisions is "aspirational," the working group should address and resolve inconsistencies to guide physicians in responding appropriately when different ethical values appear to be in conflict.

II. Conclusion

Public Citizen commends the working group on its latest effort to improve the Declaration of Helsinki through various proposed revisions. In particular, we support provisions requiring adequate compensation to subjects who are harmed as a result of participating in clinical research and consideration of benefits for the communities where research is carried out. We also support

[5] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Draft revised text for public consultation, annotated version. April 15, 2013. http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/DoH-draft-for-public-consultation_annotated.pdf. Accessed June 11, 2013.

provisions for post-trial access for research participants, efforts to strengthen the wording of various paragraphs, requirements that risks be minimized for participants throughout the trial, and clarifications regarding denial of best proven intervention in a clinical trial. We have recommended some additional changes to these proposed amendments, intended to help clarify and strengthen their effect.

Our greatest concern with the revisions is that the annotated comments to the revision proposal weaken the entire document by suggesting that one important statement — "the well-being of the individual research subject must take precedence over all other interests" — is "intended to be aspirational" and therefore need not be reconciled with the remaining provisions in the document.[6] We believe the working group should resolve inconsistencies in the document rather than encourage physicians to disregard this provision by calling it "aspirational."

Thank you for the opportunity to comment on this important document.

Sincerely,

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[6] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Draft revised text for public consultation, annotated version. April 15, 2013. http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/DoH-draft-for-public-consultation_annotated.pdf. Accessed June 11, 2013.