

**Response to WMA's "DoH Call for Comments 8/2008"  
regarding the May 2008 Consultation Draft of the  
Declaration of Helsinki**

Submitted (as invited) by:

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## A. Opening Remarks

This submission is divided into three sections (including this section “A. Opening Remarks”). Section B is a “Marked-up” copy of our suggested revisions to the May 2008 draft revision of the Declaration of Helsinki (DoH). We have followed the instructions issued by the World Medical Association (WMA) in compiling this “Marked-up” copy. Finally Section C is a commentary on each of the paragraphs where we suggest changes, presenting our reasoning behind the suggestions.

## B. “Marked-up” Changes Suggested to May 2008 Revision Draft of the Declaration of Helsinki

### THE WORLD MEDICAL ASSOCIATION, INC.

<b>WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI</b>
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<b>2004 Version DoH</b>	<b>May 2008 Consultation Draft</b>	<b>Reasons for change (our added reasons are underlined)</b>
Subtitle: Ethical Principles for Medical Research Involving Human Subjects	Subtitle: Ethical Principles for Medical Research <del>Involving</del> <u>On</u> Humans	‘Subjects’ is used in the document where appropriate. <u>All medical research somehow ‘involves’ humans – this is an attempt to achieve greater precision.</u>
A. INTRODUCTION	A. INTRODUCTION	
1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other	1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving humans, including research	This paragraph has been divided in two: the first stating the purpose and scope of the Declaration; the second specifying to whom it is addressed.

<p>participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.</p>	<p>on identifiable human material and data. <b><u>The Declaration of Helsinki is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant parts of the Declaration.</u></b></p>	<p><u>Otherwise only Paragraph 32 states this explicitly.</u></p>
	<p>2. Although the Declaration is addressed primarily to physicians, the World Medical Association invites other participants in medical research involving humans to adopt these principles.</p>	<p>Most commentators felt that the Declaration should be addressed primarily to physicians but that others should be encouraged to act according to its principles.</p>
<p>2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.</p>	<p>3. It is the duty of the physician to promote and safeguard the health of people, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.</p>	<p>The addition makes the physician's general duty relevant to the subject of the Declaration, i.e., research.</p>
<p>3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."</p>	<p>4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."</p>	<p>This change brings the Declaration into line with the current wording of the International Code that was amended in 2006.</p>
<p>4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.</p>	<p>5. Medical progress is based on research that ultimately must include studies involving humans. Populations that are underrepresented in</p>	<p>The additional sentence incorporates the suggestions of commentators. It fits well in this paragraph.</p>

	medical research should be provided appropriate access to participation in research.	
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.	6. In medical research involving humans, the well-being of the individual research subject should take precedence over all other interests.	Minor editorial changes.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.	7. The primary purpose of medical research involving humans is to understand the aetiology and pathogenesis of disease and improve preventive, diagnostic and therapeutic methods. Even the best current methods should continually be evaluated through research for their safety, effectiveness, efficiency, accessibility and quality. <b><u>Although all medical knowledge, even that considered best proven, should be challenged through research, resources for medical research are limited and the development of just procedures for prioritising research should be a matter of concern for all physicians involved in research.</u></b>	Minor editorial changes including elimination of unnecessary repetition.  'Must' has been changed to 'should' throughout the document since it is a statement of principles, not of laws or regulations.  <u>Without a statement to this effect, there is no mention of the ethical issue of prioritisation of research in the Declaration of Helsinki. See Section C.2 (above).</u>
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.	8. In medical practice and in medical research, most methods involve risks and burdens.	Minor editorial changes.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some	9. Medical research is subject to ethical standards that promote respect for all humans and protect their health and rights. Some research populations are	Minor editorial changes.

<p>research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.</p>	<p>particularly vulnerable and need special protection. These include the educationally, economically or medically disadvantaged, those who cannot give or refuse consent for themselves, <del>those who may be subject to giving consent under duress,</del> and those who may be vulnerable to coercion or undue influence.</p>	<p><u>The statements ‘subject to give consent under duress’ and ‘vulnerable to coercion or undue influence’ appear to be synonymous.</u></p> <p>The deletion of “for those who will not benefit personally from the research” incorporates the idea that, by its very nature, research cannot guarantee that subjects will benefit from the research intervention.</p>
<p>9. Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.</p>	<p>10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving humans in their own countries as well as applicable international norms and standards. No national ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.</p>	<p>Minor editorial changes.</p>
<p><b>B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH</b></p>	<p><b>B. PRINCIPLES FOR ALL MEDICAL RESEARCH</b></p>	<p>‘Basic’ is unnecessary.</p>
<p>10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.</p>	<p>11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of research subjects. <b>EVERY PRECAUTION</b></p>	<p>The additions bring together concepts that formerly were scattered throughout this section. <u>We are uncertain about the need for “of personal information” as we are uncertain as to whether there is any other kind of confidentiality.</u></p>

	<p><b><u>SHOULD BE TAKEN TO PROTECT ALL OF THE ABOVE THE PRIVACY AND CONFIDENTIALITY OF RESEARCH SUBJECTS AND TO MINIMIZE THE IMPACT OF THE RESEARCH ON THEIR PHYSICAL, MENTAL AND SOCIAL INTEGRITY.</u></b></p>	<p>Moved here from Paragraph 23 – otherwise seems repetitive. For stylistic reasons, we have also modified the text slightly (“all of the above” instead of repeating “privacy and confidentiality of research subjects”).</p>
<p>11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.</p>	<p>12. Medical research involving humans should conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research should be respected.</p>	<p>The last sentence has been moved from former para. 12 since it fits more appropriately here.</p>
<p>12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.</p>	<p>13. Appropriate caution should be exercised in the conduct of research that may affect the environment</p>	<p>Moved to para. 11</p>
	<p><b><u>13A. EVERY MEDICAL RESEARCH STUDY INVOLVING HUMANS SHOULD BE PRECEDED BY CAREFUL ASSESSMENT OF PREDICTABLE RISKS AND BURDENS TO THE INDIVIDUALS AND COMMUNITIES INVOLVED IN THE RESEARCH IN COMPARISON WITH</u></b></p>	<p>We think the process of evaluating risks and benefits and the statement of the principle that objective should outweigh risks belongs before the paragraphs regarding ethical review. Physicians should consider these things before submitting a protocol for review and the protocol should contain these considerations. Therefore we recommend</p>

	<p><b><u>FORESEEABLE BENEFITS TO THEM AND TO OTHER INDIVIDUALS OR COMMUNITIES AFFECTED BY THE CONDITION UNDER INVESTIGATION. MEDICAL RESEARCH INVOLVING HUMANS SHOULD ONLY BE CONDUCTED IF THE IMPORTANCE OF THE OBJECTIVE OUTWEIGHS THE INHERENT RISKS AND BURDENS TO THE RESEARCH SUBJECT.</u></b></p>	<p>that Paragraph 18 and Paragraph 21 be located here. We have combined them into one paragraph but would equally support them here as separate Paragraphs.</p>
<p>13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious</p>	<p>14. The design and performance of each research study involving humans should be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should 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 participation in the research study. The protocol should describe arrangements for post-study access by study subjects to methods identified as beneficial in the study or access to other appropriate care or benefits.</p>	<p>Current paragraphs 13 and 14 have been reorganized so that the protocol is dealt with in new 14 and the research ethics committee in new 15.</p> <p>The change from “that there is compliance with the principles enunciated in this Declaration” to “how the principles in this Declaration have been addressed” is intended to encourage researchers to consider carefully the ethical aspects of their research.</p> <p>The last sentence has been transferred from the note of clarification to paragraph 30, since it belongs more appropriately here.</p>

<p>adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.</p>		
<p>14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.</p>	<p>15. The research protocol should be submitted for consideration, comment, guidance and approval to a research ethics committee, which should be independent of the researcher, the sponsor and any kind of undue influence. This committee should take into consideration the laws and regulations of the <del>country or countries</del> <b><u>jurisdictions</u></b> in which the research is to be performed. The committee should have the right to monitor ongoing studies <b><u>and changes to the research protocol require approval by the committee.</u></b> The researcher should provide monitoring information to the committee, especially information about any serious adverse events. <del>No change in the protocol should be made without consideration and approval of the committee.</del></p>	<p>All research ethics committees (a more widely used term than ‘ethical review committees’) should have the authority to approve, or not approve, research protocols. If the research is to be conducted in a country or countries other than that where committee approval is sought, the committee should ensure that the research is not in conflict with the laws and regulations of the host country or countries. Such committees should exist wherever medical research is conducted and therefore should not have to be specially appointed to deal with specific protocols. <u>This suggested change shortens the text slightly without (we believe) any loss of meaning. We think that the requirement of the committee to “consider” changes before approving them goes without saying.</u></p>
<p>15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the</p>	<p>16. Medical research involving humans should be conducted only by <del>scientifically qualified</del> <b><u>suitably trained</u></b> persons under the supervision of a competent and appropriately health professional. The</p>	<p>Minor editorial changes.</p> <p><u>We consider this to be a more appropriate statement of the ethical requirement as “scientifically qualified” contains many ambiguities: see Appendix: B: Paragraph 15 for more</u></p>

<p>human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.</p>	<p>responsibility for the protection of research subjects should always rest with the physician and never the research subjects, even though they have given consent.</p>	<p><u>detailed argument.</u></p>
	<p>17. Medical research involving a disadvantaged population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.</p>	<p>Moved from current 19. The addition of “a disadvantaged population or community” allows for phase one clinical trials on diseases that primarily affect developing countries (e.g., malaria) to be conducted in developed countries.</p>
<p>16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.</p>	<p>18. EVERY MEDICAL RESEARCH STUDY INVOLVING HUMANS SHOULD BE PRECEDED BY CAREFUL ASSESSMENT OF PREDICTABLE RISKS AND BURDENS TO THE INDIVIDUALS AND COMMUNITIES INVOLVED IN THE RESEARCH IN COMPARISON WITH FORESEEABLE BENEFITS TO THEM AND TO OTHER INDIVIDUALS OR COMMUNITIES AFFECTED BY THE CONDITION UNDER INVESTIGATION.</p>	<p>The addition of communities recognizes their importance in determining the risks and benefits of a research study.</p> <p>The deleted sentence is unnecessary and in any case does not fit in here.</p> <p>The last sentence has been moved to the following paragraph.</p> <p><u>We suggest the requirements of this paragraph should precede submission for ethical review and suggest moving this to between Paragraphs 13 and 14 (shown in marked-up text as Paragraph 13A).</u></p>
	<p>19. Every clinical trial should be registered in a publicly accessible database, <b><u>or, where such databases have not been established, details of the trial should otherwise be</u></b></p>	<p>Expansion of the last sentence of the previous paragraph, as suggested by commentators.</p> <p><u>Without this change, does this not assume that all jurisdictions have already</u></p>

	<b><u>made publicly available,</u></b> before recruitment of the first subject.	<u>set up such databases? Is that a reasonable assumption?</u>
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.	20. Physicians should not participate in a research study unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation as soon as the risks are found to outweigh the potential benefits or as soon as there is conclusive proof of positive and beneficial results.	Minor editorial changes.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.	21. MEDICAL RESEARCH INVOLVING HUMANS SHOULD ONLY BE CONDUCTED IF THE IMPORTANCE OF THE OBJECTIVE OUTWEIGHS THE INHERENT RISKS AND BURDENS TO THE RESEARCH SUBJECT.	The principle applies equally to all research subjects. Healthy volunteers are no different in this respect. <u>This should be considered when physicians are developing the protocol and the case made to, and evaluated by, the ethics committee, therefore moved to paragraph 13A.</u>
19. 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.		Moved to 17.
20. The subjects must be volunteers and informed participants in the research project.	22. Participation by legally competent individuals in medical research involving humans must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual should be enrolled in a research study unless he or	The first change allows for involuntary participation in research by incompetent individuals as governed by paragraphs 27-29.  The additional sentence addresses the custom in some populations whereby the competent individual's agreement to participate in

	she freely agrees.	research may need to be supplemented, but never replaced, by the agreement of another person.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.	23. EVERY PRECAUTION SHOULD BE TAKEN TO PROTECT THE PRIVACY AND CONFIDENTIALITY OF PERSONAL INFORMATION OF RESEARCH SUBJECTS AND TO MINIMISE THE IMPACT OF THE STUDY ON THEIR PHYSICAL, MENTAL AND SOCIAL INTEGRITY.	Minor editorial changes. The deleted sentence is covered in para.10. <u>This first part is very repetitive of Paragraph 11 so we suggest it be slightly modified and moved along with the intact 2<sup>nd</sup> part to the end of paragraph 11.</u>
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally	24. In medical research involving legally competent human subjects, each potential subject should be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject should be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the	Incompetent potential research subjects are dealt with in paragraphs 27-29. The term 'potential subject' is used to indicate that an individual does not become a 'subject' until consent is given.  This addition was suggested by commentators.  'Obtain' has been changed to 'seek' to emphasize the potential subject's right to either refuse or agree to take part in the research.

<p>documented and witnessed.</p>	<p>information, the physician should then seek the potential subject’s freely-given informed consent, preferably <b><u>expressed</u></b> in writing. If the consent cannot be expressed in writing, the non-written <b><u>expression of</u></b> consent should be formally documented and witnessed.</p>	<p><u>This addresses our concerns that it is not “written consent” (i.e., it is not a legal contract) but “written evidence of consent” but we think the word expressed should be used in all instances to emphasise this.</u></p>
	<p>25. For medical research using human tissues or data, physicians should seek consent for the collection, investigation, storage and reuse of samples. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research should be done only after consideration and approval of a research ethics committee.</p>	<p>New paragraph to deal with informed consent in research using human tissues or data.</p>
<p>23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.</p>	<p>26. When seeking informed consent for participation in the research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under <b><u>coercion or undue influence</u></b>. In that case the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.</p>	<p>Minor editorial changes.</p> <p>Another physician may not be available to perform this task.</p> <p><u>This phrase is used elsewhere in the DoH and we think is better wording than “duress”.</u></p>
<p>24. For a research subject who is legally incompetent, physically or mentally incapable of</p>	<p>27. For a potential research subject who is legally incompetent, the physician should seek informed</p>	<p>Potential research subjects who are physically or mentally incapable of giving consent but who are</p>

<p>giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.</p>	<p>consent from the legally authorized representative in accordance with applicable law. These individuals should not be included in a research study unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with legally competent persons, and the research entails only minimal risk and minimal burden in the absence of benefit for the potential subject.</p>	<p>not legally incompetent are dealt with in para. 29.</p> <p>Additional protection for these individuals while allowing higher risk research interventions that can benefit the research subjects.</p>
<p>25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.</p>	<p>28. When a potential research subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the physician should seek that assent in addition to the consent of the legally authorized representative.</p>	<p>Minor editorial changes.</p>
<p>26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol</p>	<p>29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, should 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 seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the</p>	<p>Rewording for the purpose of clarification.</p>

<p>should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate</p>	<p>specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol, <b><u>that proceeding in such circumstances is legal in the jurisdiction concerned</u></b> and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.</p>	<p><u>See our discussion in Section B.1.36 above.</u></p>
<p>27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.</p>	<p>30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors are accountable for the accuracy of the results. They have a duty to make publicly available the results of their research on humans. In so doing they should adhere to accepted guidelines for ethical reporting. Negative (<b><u>i.e., both adverse results and findings that show no difference between experimental and established methods</u></b>) as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and <b><u>potential</u></b> conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.</p>	<p>Rewording for the purpose of clarification.</p> <p><u>We are uncertain of the best wording here and make this tentative suggestion. See our discussion in Section C.5 (above).</u></p> <p><u>Authors should declare “potential” conflicts of interest (as is also required in Paragraph 14): publishers and/or readers can decide whether there is an actual conflict that may affect their interpretation of the research.</u></p>

<p>C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE</p>	<p>C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE</p>	
<p>28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.</p>	<p>31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects. When medical research is combined with medical care, the following additional standards apply to protect these patients.</p>	<p>Additional protection for research subjects.</p>
<p>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.</p> <p><b>Note of clarification</b></p> <p>The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy.</p>	<p>32. The benefits, risks, burdens and effectiveness of a new method should be tested against <del>either those of the best proven</del> <b><u>or widely used</u></b> current methods, <b><u>depending on the aims of the study. Such aims must conform to all requirements of the Declaration of Helsinki.</u></b></p> <p><b><u>Extreme care must be taken in making use of a placebo-controlled trial and, in general, this methodology should only be used in the absence of existing methods.</u></b></p> <p>except in the following circumstances:</p> <p><del>—The use of placebo, or no treatment, is acceptable in studies where no proven current method exists or:</del></p> <p><del>—Where for compelling and</del></p>	<p>The contents of the note of clarification have been incorporated in the paragraph with no changes to the requirements. In this way, the apparent contradiction between the paragraph and the note, that some commentators allege, disappears.</p> <p>The inconsistency between ‘best current’ and ‘proven’ method has been resolved by using the term, ‘best proven current method’.</p> <p><u>Please see Section C.1 above for a full discussion of our reasoning behind these suggestions.</u></p>

<p>However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:</p> <ul style="list-style-type: none"> <li>- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or</li> <li>- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.</li> </ul> <p>All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.</p>	<p>scientifically sound methodological research the use of a placebo is necessary to determine the efficacy and safety of a method and the patients who receive placebo or no treatment will not be subject to any additional risk of serious or irreversible harm.</p> <p><b><u>Where such methods do exist, the use of placebo, or no treatment, may be justified, provided all of the following conditions are met in the opinion of the researchers and following especially careful and detailed scrutiny by the independent ethical review committee:</u></b></p> <ul style="list-style-type: none"> <li>- <b><u>there are compelling scientific and methodological reasons why a placebo-controlled design is necessary;</u></b></li> <li>- <b><u>that because of the nature of the condition under study, there is a reasonable likelihood that research subjects will personally benefit in the future from advances made in the understanding and treatment of their condition;</u></b></li> <li>- <b><u>the research design is such that any risks of serious or long-lasting harm to participants are both minimal and proportionate to the potential benefits of the study;</u></b></li> <li>- <b><u>that as part of the study participants are monitored sufficiently closely that</u></b></li> </ul>	
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	<p><b><u>any evidence of possible harm occurring as a result of participating in the research is detected as early and possible, and, should this occur, that any ‘blinding’ of patient and physician responsible for the care of the patient as to what the patient is receiving is removed and the patient is then offered the most appropriate active treatment with no unnecessary delay, irrespective of any effect this may have on the scientific validity of the study;</u></b></p> <p><b><u>- that particular attention be paid to ensuring that when informed consent is sought that there will be no misunderstanding on the part of participants about the fact that they may receive an inactive placebo or no treatment despite the existence of proven or widely available active treatment and that participants’ agreement to take part will be free of any coercion or deception about these facts;</u></b></p> <p><b><u>- that the use of placebo-controls has not been justified on the basis that participants have come from a population where, despite the existence of active methods, that such methods are generally unavailable in that population.</u></b></p>	
<p>30. At the conclusion of the study, every patient entered into the study should be assured of</p>	<p>33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome</p>	<p>The requirement in the current paragraph is covered by the last sentence of paragraph 14.</p>

<p>access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.</p> <p>Note of clarification</p> <p>The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.</p>	<p>of the study. <b><u>At the time of obtaining informed consent for participation, and at any time during the study if the probable situation at the end of the study changes, patients should be fully informed about what is likely to happen at the end of the study with respect to access to study methods that appear to be benefiting them personally, and where such methods may not be available, what other appropriate care will be available.</u></b></p>	<p><u>We feel the requirement to inform about outcome is a very inadequate statement of the duty of care to patients (in contrast to healthy volunteers etc.) at the end of a study.</u></p> <p>The last sentence of the note of clarification has been moved to paragraph 14.</p>
<p>31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.</p>	<p>34. The physician should fully inform the patient which aspects of the care are related to the research. <b><u>A patient's</u></b> <del>The refusal of a patient to participate in a study or the patient's decision to</del> <b><u>subsequently</u></b> withdraw from <del>the a</del> study should never interfere with the patient-physician relationship.</p>	<p>Addition suggested by commentators. <u>A suggestion as to how the same could be said with fewer words.</u></p>
<p>32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic</p>	<p>35. In the treatment of a patient, where proven methods do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven or new method if in the physician's judgement it</p>	<p>Addition suggested by commentators.</p> <p><u>We argue that there should</u></p>

<p>measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.</p>	<p>offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this method should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available. <del>The other relevant guidelines of this Declaration should be followed.</del></p>	<p><u>be a more general statement that the DoH should be read as a whole and interpreted in the light of all relevant paragraphs and that such a statement should not be confined to one paragraph only (unless it is Paragraph 1). See Section C.2 (above).</u></p>
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### C. Comments Regarding Suggested Changes

#### Subtitle

The phrase “Medical Research Involving Humans” is ambiguous, since all medical research involves humans in some way. “Ethical Principles for Medical Research On Humans”, used in the proposed paragraph 30 regarding publication ethics, would be a better alternative.

#### Paragraph 7

While the intent of the proposed paragraph 7 that all methods be continually challenged according to the criteria of safety etc. is commendable, it is of concern that there is no mention in the Declaration of Helsinki of the ethical requirement to prioritise research. Even though all methods should remain open to challenge through research, that does not mean that all methods are equally needful of being the *next issue to be researched*. Research resources are finite and some attention should be given to deciding how best to allocate such resources in terms of the potential health gains they will achieve.

#### Paragraph 10

While the wording of this paragraph may not need to be changed, it is of concern that the implications of this paragraph (altered significantly in the 5<sup>th</sup> (Edinburgh, 2000) revision), i.e., that “No national ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration”, have not have not fully worked their way through the rest of the Declaration of Helsinki.

### **Paragraph 16**

The phrase “scientifically qualified” is obscure and potentially inaccurate. It is competence, based on adequate training that is the issue here. A better wording would be: “Clinical research involving human subjects should be conducted only by suitably trained persons under the supervision of a competent health professional”.

### **Paragraph 19**

Problems could be raised by the requirement in paragraph 19 – that all trials be registered in a publicly available database. This presumes that such databases have been set up in the jurisdiction concerned. While details of the planned trial should be made publicly available before recruitment, might this requirement hinder the conduct of potentially beneficial research in places where no such databases have yet been established?

### **Paragraph 29**

While it is ethically appropriate to proceed with the research provided all of the criteria are met, this paragraph could be improved by including a phrase such as “and the inclusion of such subjects is permitted under local laws or regulations”. Some jurisdictions explicitly permit such research [e.g., Adults with Incapacity (Scotland) Act 2000] but where such is not legally permitted it should not be embarked upon.

### **Paragraph 32**

In the light of discussion about the ethical aspects of placebo-controlled trials, as well as the appropriate standard of control arm in clinical trials, in relation to some of the most disputed aspects of the 5<sup>th</sup> (Edinburgh, 2000) revision of the Declaration of Helsinki, some version of the following might helpfully replace this paragraph.

The benefits, risks, burdens and effectiveness of a new method should be tested against either the best proven or widely used current methods, depending on the aims of the study. The choice of treatment arm will depend on the aims of the study and such aims must conform to all requirements of the Declaration of Helsinki. Extreme care must be taken in making use of a placebo-controlled trial and, in general, this methodology should only be used in the absence of existing methods. Where such methods do exist, the use of placebo, or no treatment, may be justified, but only provided that all of the following conditions are met both in the opinion of the researchers and following especially careful and detailed scrutiny by the independent ethical review committee:

- the case has been made that there are compelling scientific and methodological reasons why a placebo-controlled design is necessary and that no other research method could lead to adequate testing of the hypothesis under consideration
- that by virtue of the nature of the condition under study, there is a reasonable likelihood that the research subjects stand to benefit personally from advances made in the understanding and treatment of their condition
- the research design is such that any risks of any serious or long-lasting harm to participants are both minimal and proportionate to the potential benefits of the study

- that as part of the study, participants are monitored sufficiently closely that any evidence of possible harm occurring as a result of participating in the research is detected as early as possible, and, should this occur, that any ‘blinding’ of patient and the physician responsible for the care of the patient as to what the patient is receiving is removed, and the patient is then offered the most appropriate active treatment with no unnecessary delay, irrespective of any effect this may have on the scientific validity of the study
- that particular attention be paid to ensuring that when informed consent is sought that there will be no misunderstanding on the part of participants about the fact that they may receive an inactive placebo or no treatment despite the existence of proven or widely available active treatment and that participants’ agreement to take part will be free of any coercion or deception about these facts
- that the use of placebo-controls has not been justified on the basis that participants have come from a population where, despite the existence of active methods, that such methods are generally unavailable in that population.

**Paragraph 33**

It is troubling that the post-trial duty of care to patients enrolled in a study – at least as it is articulated in this section – has been reduced to an entitlement to be informed about the results of the study. Even if it decided to retain the requirement to spell out in the protocol the post-trial access to care in the “Basic Principles for All Medical Research” (Paragraph 14 in the proposed revision), rather than in this section (where it is most appropriate) this paragraph is inadequate. At the very least, it should add to the entitlement to know the outcome, a requirement along the lines of: “At the time of obtaining informed consent for participation, and at any time throughout the study if the probable situation at the end of the study changes, patients should be fully informed about what is likely to happen at the conclusion of the study with respect to their access to study methods that appear to be benefiting them personally, and where such methods may not be available, what other appropriate care will be available”.