Declaration of Helsinki 2022-2024 Revisions

Recommendations of the WMA Workgroup on the Revision of the Declaration of Helsinki
as forwarded to the WMA Council on October 14, 2024

The Workgroup rationales and descriptions of proposed changes are included before each paragraph.

Underneath the rationale, the left-hand column shows the existing language from the 2013 revision, and the right-hand column shows the proposed text from the Workgroup. Additions are **bolded and underlined**, while deletions are indicated by ~~strikethrough~~.

WMA Declaration of Helsinki
Ethical Principles for Medical Research Involving Human ~~Subjects~~**Participants**

Preamble

Paragraph 1
The Workgroup proposed replacing "subjects" with "participants" throughout the DoH out of respect for the rights, agency, and importance of those individuals. Public comments in both periods one and two welcomed the change.

2013 DoH Language:	**Workgroup Proposal:**
1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.	1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human ~~subjects~~ **participants**, including research **using** ~~on~~ identifiable human material ~~and~~ **or** data. The Declaration is intended to be read as a whole, and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

Paragraph 2

*In public comment period one, the Workgroup proposed replacement language acknowledging the interdisciplinary nature of medical research and the frequency with which physicians lead large teams. The Workgroup strongly believes that **all** participants in medical research must share in the protections afforded by the DoH regardless of who is conducting or helping to conduct the research. The proposed language also recognizes that participants in medical research include both patients and healthy volunteers.*

Period one and period two public comments largely supported paragraph 2 applying to all researchers and not just physicians. Comments also highlighted that many nonphysicians have contributed to writing the DoH (ethicists, etc.), and that organizations play important roles in addition to individuals and teams, so edits were made to reflect those points.

The Workgroup also made edits based upon public suggestions to reorder the phrases in the sentence for clarity.

The Workgroup also proposed adding "respect for" to "protection of" to emphasize the agency of participants.

Several public comments also asked whether "medical research" should be broadened to "health research" throughout the Declaration, or reworded to otherwise include non-medical or socio-behavioral research involving humans. However, the Workgroup is not recommending that change now due in part to the very broad nature of health research.

2013 DoH Language:	**Workgroup Proposal:**
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.	~~Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.~~ **2. While the Declaration is adopted by physicians, the WMA holds that these principles should be upheld by all individuals, teams, and organizations involved in medical research, as these principles are fundamental to respect for and protection of all research participants, including both patients and healthy volunteers.**

General Principles

Paragraph 3

<table>
<tr><td colspan="2">Public comments during period two noted that the Declaration of Geneva and the International Code of Medical Ethics had undergone their own revisions since the last revision of the Declaration of Helsinki, and that the quoted text in paragraph 3 was no longer up to date. Therefore, the Workgroup has updated this paragraph to accurately reflect these source documents.</td></tr>
<tr><td>2013 DoH Language:
3. 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.”</td><td>Workgroup Proposal:
3. The <u>WMA</u> Declaration of Geneva ~~of the WMA~~ binds the physician with the words, “The health <u>and well-being</u> of my patient will be my first consideration,” and the <u>WMA</u> International Code of Medical Ethics declares, ~~that~~ <u>“The physician must commit to the primacy of patient health and well-being and must offer care in the patient’s best interest.”</u> ~~A physician shall act in the patient’s best interest when providing medical care~~</td></tr>
<tr><td colspan="2">Paragraph 4
No proposed changes.</td></tr>
<tr><td>2013 DoH Language:
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.</td><td>Workgroup Proposal:
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty. [No proposed changes]</td></tr>
<tr><td colspan="2">Paragraph 5
The Workgroup proposed moving the last sentence of the 2013 version paragraph 6 (regarding continuous evaluation of best proven interventions) up to the end of paragraph 5. Within the relocated sentence, the Workgroup agreed with period one public comment suggestions to change “must” to “should” given that researchers cannot continuously evaluate all of the hundreds of thousands of medical therapies in use.

Public comments from period two noted that the need for ongoing evaluation should apply to many therapies in use (not just the best proven ones), so the Workgroup proposed changing “the best proven” to “well-proven.”

A public comment from period two considered whether “continually” might be replaced with “periodically” to more accurately describe the reality of repeating research, but the Workgroup is not recommending that change at this time.</td></tr>
</table>

2013 DoH Language: 5. Medical progress is based on research that ultimately must include studies involving human subjects.	**Workgroup Proposal:** 5. Medical progress is based on research that ultimately must include ~~studies involving~~ human ~~subjects~~ **participants**. Even ~~the best~~ **well-proven** interventions ~~must~~ **should** be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality. *[Moved up from paragraph 6 of the 2013 version]*

Paragraph 6

The Workgroup received many suggestions during public comment period one to move paragraph 7 on ethical standards (from the 2013 version) up and place it before paragraphs 6 and 8 on purposes of research (from the 2013 version) for continuity. The 2013 paragraph 7 now appears here as paragraph 6 (i.e., reordered to prior 7, prior 6, prior 8).

Based on feedback heard at regional and topical meetings, especially the Vatican and Johannesburg meetings, the Workgroup also proposed a new aspirational sentence about global justice, which acknowledges structural inequities and urges researchers to carefully consider where and with whom research is carried out (while not calling upon the research enterprise to single-handedly solve all health inequities).

New language about the importance of meaningful engagement with potential participants and their communities was also proposed by the Workgroup in response to many thoughtful comments at regional meetings, especially the Vatican and Johannesburg meetings, about the importance of community engagement. This addition has received substantial support from public comments and subsequent regional/topical meetings in support of seeing participants and communities as partners and co-creators of research.

The Workgroup had initially proposed the word "empower" in the final sentence, and then reflected on period two public comments in support of replacing it with another word. The Workgroup ultimately recommended the word "enable" instead. The Workgroup discussed a comment made by one speaker in Washington that the word "enable" might still perpetuate a power differential that puts research participants in a dependent position. However, while the Workgroup strongly agrees that participants and communities should share in power, it also felt that it would be inaccurate to imply that researchers did not need to take active steps to enable potential and enrolled participants and their communities to participate in research design, implementation, and dissemination.

The Workgroup discussed period two public comments suggesting that "where feasible" might be added to patients/communities participating in study design and implementation, but did not vote to insert that qualifying language at this time because of a desire to send a strong signal on the issue of community engagement.

2013 DoH Language:	**Workgroup Proposal:**
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.	~~7.~~ **6.** Medical research **involving human participants** is subject to ethical standards that promote and ensure respect for all ~~human subjects~~ **participants** and protect their health and rights. **Since medical research takes place in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens are distributed.** **Meaningful engagement with potential and enrolled participants and their communities should occur before, during, and following medical research. Researchers should enable potential and enrolled participants and their communities to share their priorities and values; to participate in research design, implementation, and other relevant activities; and to engage in understanding and disseminating results.**

Paragraph 7

In public comment period one, based upon feedback from regional meetings, the Workgroup initially proposed specific mention of "social value," including individual and public health, as additional primary purposes of conducting medical research. However, the Workgroup received many public comments expressing concern with the vagueness of the proposed term "social value." The Workgroup therefore proposed additional edits below based on public suggestions to newly reference advancing "individual and public health" without using the term social value. This still speaks to the idea that the scientific purposes of medical research on human participants must be considered hand in hand with their ultimate value in advancing health.

Period two public comments on the last sentence of this paragraph (from former paragraph 8) ranged from some urging the Workgroup to remove or soften the language on the primacy of individual participant rights, to others pressing the Workgroup to maintain or even strengthen it. The Workgroup is not proposing to substantively change this sentence on the precedence of the rights and interests of individual research participants, especially given the historical abuses that led to the writing of this Declaration. However, the Workgroup does recognize that participants with free and informed consent do sometimes choose to participate in trials where the benefits primarily or solely accrue to others, and that is part of the rationale for addition of language on advancing both individual and public health.

The Workgroup also received many suggestions during public comment period one to move paragraphs 6 and 8 (from the 2013 version) together given their relationship to each other, so they were combined and harmonized here as proposed new paragraph 7.

The Workgroup also proposed moving the last sentence of 2013 paragraph 6 about continuous evaluation of the best proven interventions up to paragraph 5, so it no longer appears here.

2013 DoH Language: 6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality. 8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.	**Workgroup Proposal:** ~~6.~~ **7**. The primary purpose of medical research involving human ~~subjects~~ **participants** is to **generate knowledge to** understand the causes, development and effects of diseases**;** ~~and~~ improve preventive, diagnostic and therapeutic interventions ~~(methods, procedures and treatments)~~**; and ultimately to advance individual and public health.** ~~Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.~~ *[Final sentence moved up to paragraph 5]* ~~8.While the primary purpose of medical research is to generate new knowledge, this goal~~ **These purposes** can never take precedence over the rights and interests of individual research **participants** ~~subjects~~.
Paragraph 8 *The Workgroup proposed this new paragraph based on recommendations at regional meetings (especially at the Tokyo meeting) in the wake of the COVID-19 pandemic to state clearly that public health emergencies do not reduce the importance of DoH principles.*	
2013 DoH Language: N/A	**Workgroup Proposal:** **8. While new knowledge and interventions may be urgently needed during public health emergencies, it remains essential to uphold the ethical principles in this Declaration during such emergencies.**
Paragraph 9 *Consistent with proposed updated paragraph 2 stating that the Declaration's principles should be upheld by **all** involved in medical research, and in response to several public comments, the Workgroup proposed the following approach for consistently describing those engaged in research throughout the DoH:* • *The Workgroup establishes and emphasizes its overarching opinion in Paragraph 2 that the principles in the DoH "should be upheld by all individuals, teams, and organizations involved in medical research."* • *When discussing core ethical responsibilities of physicians as members of the medical profession (as in paragraphs 3 and 4, and the first sentence of paragraph 9 here), the Workgroup has maintained references to physicians.* • *When discussing the rights of participants and associated ethical responsibilities of all those engaged in research (as in the second sentence of paragraph 9 here and many other points later in the Declaration), the Workgroup proposes consistent use of "physicians or other*	

researchers," to acknowledge that these rights and responsibilities apply regardless of the training/profession of the researcher or research team member. The Workgroup has accepted period two public comment recommendations to remove the term "qualified researcher" that it earlier proposed, as these responsibilities apply regardless of whether a researcher is qualified.

- *When discussing the steps required of those obtaining freely informed consent (as in Paragraph 26), the Workgroup proposes consistent use of "the physician or another qualified individual," since the person obtaining free and informed consent may not always formally be a researcher but must be qualified to fully inform the potential participant and answer questions.*

Public feedback about these changes has been largely positive.

The Workgroup agreed with period two public comments suggesting that "autonomy" be added to the list in this paragraph, and also recommends removing "right to self-determination" because it is an aspect of autonomy.

2013 DoH Language:	**Workgroup Proposal:**
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.	9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, ~~right to self-determination,~~ **autonomy**, privacy, and confidentiality of personal information of research **participants** ~~subjects~~. The responsibility for the protection of research **participants** ~~subjects~~ must always rest with ~~the~~ physician**s** or other **researchers** ~~health care professionals~~ and never with the research **participants** ~~subjects~~, even though they have given consent.

Paragraph 10

See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physicians and other researchers" here.

*This paragraph has been updated to require following norms and standards in the country where the research originated **and** where it is to be performed, consistent with the proposed edits to paragraph 23 which would require host country ethics committee approval for international research.*

2013 DoH Language:	**Workgroup Proposal:**
10. Physicians 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. 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.	10. Physicians **and other researchers** must consider the ethical, legal and regulatory norms and standards for research involving human **participants** ~~subjects in their own countries~~ **in the country or countries in which the research originated and where it is to be performed,** as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research **participants** ~~subjects~~ set forth in this Declaration.

Paragraph 11 *In public comment period one, the Workgroup proposed language to further emphasize considering the environmental impacts of medical research when designing studies, using sustainability language consistent with recent revisions to the WMA's International Code of Medical Ethics (ICoME).* *Many period one public comments supported additional emphasis on the environment but advised deletion of the word "possible" from the 2013 version and expressed concern about vagueness of the new phrasing "promotes sustainability" that was proposed in public comment period one. The Workgroup deleted "possible," withdrew "and promotes sustainability," and proposed adding "designed and" and "avoids or" to strengthen this paragraph.* *Several period two comments expressed disappointment with the complete removal of "and promotes environmental sustainability." The Workgroup agreed with adding back a mention of environmental sustainability, but given differing interpretations of the word "promotes," instead proposed "strives for."*	
2013 DoH Language: 11. Medical research should be conducted in a manner that minimises possible harm to the environment.	**Workgroup Proposal:** 11. Medical research should be **designed and** conducted in a manner that **avoids or** minimizes ~~possible~~ harm to the environment **and strives for environmental sustainability.**
Paragraph 12 *Since Paragraph 2 now already explains early in the Declaration that "participants" includes both patients and healthy volunteers, the Workgroup recommended simplifying the language to just "Such research" in the second sentence here.* *The Workgroup reviewed several period 2 comments in response to paragraph 21 (which addresses research conforming to scientific principles) noting that the Declaration lacked any reference to abstaining from scientific/research misconduct. The Workgroup agreed that new language should be added on scientific integrity and research misconduct, but felt that it fit best here in paragraph 12. The Workgroup proposes new language below.* *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other researcher."*	
2013 DoH Language: 12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a	**Workgroup Proposal:** 12. Medical research involving human **participants** ~~subjects~~ must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. **Such r**esearch ~~on patients or healthy volunteers~~ requires the

competent and appropriately qualified physician or other health care professional.	supervision of a competent and appropriately qualified physician or other **researcher**. ~~health care professional.~~ **Scientific integrity is essential in the conduct of medical research involving human participants. Involved individuals, teams, and organizations must never engage in research misconduct.**
Paragraph 13 *No proposed change.*	
2013 DoH Language: 13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.	**Workgroup Proposal:** 13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research. [**No proposed change**]
Paragraph 14 *The Workgroup discussed comments at the regional meeting in Washington regarding whether this paragraph was too discouraging of research on one's own patients, whether it should be rewritten to even **require** physicians inform their patients about research opportunities, and whether the current language suggests participants are not equal partners. Because of the unique vulnerabilities patients can experience when their own physicians or health care professionals are carrying out research and recommend participating in it, the Workgroup felt this protection should remain clear, and that the current language suggests appropriate equipoise.*	
2013 DoH Language: 14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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.	**Workgroup Proposal:** 14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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 **participants.** ~~subjects~~

Paragraph 15	
2013 DoH Language: 15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.	**Workgroup Proposal:** 15. Appropriate compensation and treatment for **participants** ~~subjects~~ who are harmed as a result of participating in research must be ensured.
Risks, Burdens, and Benefits	
Paragraph 16	
2013 DoH Language: 16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.	**Workgroup Proposal:** 16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human **participants** ~~subjects~~ may only be conducted if the importance of the objective outweighs the risks and burdens to the research **participants.** ~~subjects~~
Paragraph 17 *The Workgroup noted period 2 public comments suggesting consistent use of "risks and burdens" and recommends the additions below and elsewhere in the Declaration.*	
2013 DoH Language: 17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.	**Workgroup Proposal:** 17. All medical research involving human **participants** ~~subjects~~ must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.	Measures to minimize the risks **and burdens** must be implemented. The risks **and burdens** must be continuously monitored, assessed, and documented by the researcher.
Paragraph 18 *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physicians and other researchers" here.* *The Workgroup noted period 2 comments suggesting consistent use of "risks and burdens" and recommends the additions below.* *The Workgroup has replaced "study" with "research" throughout the Declaration for consistency.*	
2013 DoH Language: 18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.	**Workgroup Proposal:** 18. Physicians **and other researchers** may not **engage** ~~be involved~~ in ~~a~~ research ~~study~~ involving human **participants** ~~subjects~~ unless they are confident that the risks **and burdens** have been adequately assessed and can be satisfactorily managed. When the risks **and burdens** are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians **and other researchers** must assess whether to continue, modify or immediately stop the **research.** ~~study~~
~~**Vulnerable Groups and Individuals**~~ **Individual, Group, and Community Vulnerability** *The Workgroup proposed amending this section title to use the word "vulnerability" rather than "vulnerable" and to call out individual, group, and community-level vulnerability. This change addresses feedback from regional and topical meetings (especially at the Vatican and in Johannesburg and Munich) that vulnerability may be contextual and dynamic and experienced at varying levels.*	
Paragraph 19 *Based on extensive feedback from many regional and topical meetings, the Workgroup proposed substantial edits to paragraphs 19 and 20 to update the Declaration's statements on vulnerability.*	

The first sentence of updated paragraph 19 addresses the contextual and dynamic nature of vulnerability (as discussed at the regional meeting in Johannesburg) and maintains language about a greater risk of being wronged or incurring harm. The Workgroup feels that clear acknowledgement of this risk is essential given the historical wrongs and abuses that led to this Declaration.

*The second sentence adds a new acknowledgement that exclusion from research can exacerbate disparities (as discussed at several regional and topical meetings) and thus carries its own risk. The third sentence adds that because both inclusion and exclusion of those with vulnerability carries risks, those harms must be considered and balanced against each other. Together, these additions respond to public feedback that the prior version of this paragraph emphasized exclusion as a default rather than responsible inclusion with protections, and that this caused harm by perpetuating and exacerbating inequities. However, acknowledging the very real risks of some **particularly** vulnerable populations being wronged or harmed, and the abuses that led to the Declaration, the Workgroup retains three specific strong protections for such populations (now addressed in paragraphs 20 and 28).*

The fourth sentence reinforces the need for specifically considered protections using the language "responsible inclusion," which was offered during the topical meeting in Munich. The Workgroup also agreed with comments from the regional meeting in Washington that "support" for those with vulnerability is a critical element to actually achieving responsible inclusion.

2013 DoH Language:	**Workgroup Proposal:**
19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.	~~19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.~~ **19. Some individuals, groups, and communities are in a situation of more vulnerability as research participants due to factors that may be fixed or contextual and dynamic, and thus are at greater risk of being wronged or incurring harm. When such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their disparities. Therefore, the harms of exclusion must be considered and weighed against the harms of inclusion. In order to be fairly and responsibly included in research, they should receive specifically considered support and protections.**

Paragraph 20

*While revised paragraph 19 address **all** individuals, groups, and communities with vulnerabilities, seeking responsible inclusion through specially considered support and protections, revised paragraph 20 retains three more restrictive protections for individuals, groups, and communities in situations of **particular** vulnerability.*

However, consistent with the spirit of changes to paragraph 19, the Workgroup added that the one existing requirement that the research can only be done if it cannot be carried out in a less vulnerable group or community should not apply if excluding the particularly vulnerable group or community would perpetuate or exacerbate their own disparities (for example, by cementing our ongoing deficit of information about drug efficacy and risks in children).

The Workgroup changed the term "non-vulnerable" to "less vulnerable" in response to participants in the regional meeting in Washington who pointed out that almost no participants have zero vulnerability.

2013 DoH Language:	**Workgroup Proposal:**
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.	~~20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.~~ 20. **Medical research with individuals, groups, or communities in situations of particular vulnerability is only justified if it is responsive to their health needs and priorities and the individual, group, or community stands to benefit from the resulting knowledge, practices, or interventions. Researchers should only include those in situations of particular vulnerability when the research cannot be carried out in a less vulnerable group or community, or when excluding them would perpetuate or exacerbate their disparities.**

Scientific Requirements and Research Protocols

Paragraph 21

In public comment period one, the Workgroup proposed new language to emphasize the ethical importance of ensuring scientifically sound design in response to concerns raised at several regional meetings about research waste consuming resources and subjecting participants to risk without any chance of providing useful information. The Workgroup emphasized that this addition would not prohibit well-designed research with low odds of a positive result (such as important clinical trials to test candidate compounds for oncology therapies).

In public comment period two, the Workgroup proposed incorporating suggestions from prior public comments to add "and execution" and to change "information" to "knowledge." The Workgroup also added specific mention of "research waste" based upon period one public feedback about the harms to participants in studies that have no chance of advancing health due to poor design. Commenters also felt "rigorous" was important to add after "sound."

The Workgroup discussed comments from period two suggesting use of the term "social value" in this paragraph, but did not make that addition here since the term was removed from paragraph 7's proposed changes after public comment period 1.

The Workgroup reviewed several period 2 comments in response to paragraph 21 noting that the Declaration lacks any reference to abstaining from scientific/research misconduct. The Workgroup agreed, but felt that such a reference fits best in paragraph 12 on qualifications of researchers, rather than here in paragraph 21 on research protocols and design. See proposed changes in paragraph 12.

The Workgroup considered concerns raised by some participants at the regional meeting in Washington about the use of "must" in the first sentence, and others suggesting the need to clarify that this responsibility lies solely with the researcher and not ethics committees or others. The Workgroup feels strongly that these are core requirements of the research enterprise and recommends retaining the current language, including the word "must."

2013 DoH Language:	**Workgroup Proposal:**
21. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.	21. Medical research involving human ~~subjects~~ **participants must have a scientifically sound and rigorous design and execution that are likely to produce reliable, valid, and valuable knowledge and avoid research waste. The research** must 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 must be respected.

Paragraph 22

The Workgroup deleted "institutional affiliations" because it is already covered by "conflicts of interest." The Workgroup also added to the list of items in the protocol to include the qualifications of the researcher. The Workgroup also recommends the addition of provisions to protect privacy and confidentiality be included in the protocol given the importance of these risk mitigations required in paragraph 24. The Workgroup made additional refinements to the list of items that should be in the protocol (here in paragraph 22) and reordered it for consistency with the list of items in informed consent in paragraph 26.

The Workgroup recommends changing "study" to "research" for consistency across the Declaration.

2013 DoH Language: 22. The design and performance of each research study involving human subjects must be clearly described and justified 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, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.	**Workgroup Proposal:** 22. The design and performance of ~~each~~ **all medical** research ~~study~~ involving human **participants** ~~subjects~~ must be clearly described and justified 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 **aims, methods, anticipated benefits and potential risks and burdens, qualifications of the researcher, sources of funding, any potential conflicts of interest, provisions to protect privacy and confidentiality, incentives for participants, provisions for treating and/or compensating participants who are harmed as a consequence of participation, and any other relevant aspects of the research.** ~~funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study~~ In clinical trials, the protocol must also describe ~~appropriate arrangements for~~ **any** post-trial provisions**.**
Research Ethics Committees	
Paragraph 23 *In public comment period one, the Workgroup proposed edits in response to feedback at regional meetings that some ethics committees face challenges performing their duties in light of the increasing volume and complexity of research and variability in resource support for the committees. The Workgroup proposed language to clarify that ethics committees must have sufficient resources, and added specificity to the qualifications of its members and staff.* *In response to public comments from period one, the Workgroup proposed broadening the requirements for ethics committees to include adequate "education, training, qualifications," mirroring the requirements for researchers in paragraph 12. The Workgroup also incorporated a suggestion from commenters to include "diversity." The Workgroup proposed adding language about committee understanding of local context and strengthened the undue influence section.*	

The Workgroup also proposed new text based on feedback at regional meetings about requiring that international research be approved in host countries (not only sponsor countries). *In the final section of the paragraph, the Workgroup responded to public comments suggesting additional language that ethics committees must be able to change or suspend studies (not just monitor them), and that committees can and do utilize external monitoring entities.* *The Workgroup reviewed period 2 comments suggesting explicit mention of ethics committees including patient representatives, community members, or the public. The Workgroup initially recommended adding that the committee must "include community members," but additional feedback at the regional meeting in Washington was that "community members" in this context was unclear and could have different regional interpretations. Therefore, the Workgroup updated the language to call for inclusion of a "member of the general public" on research ethics committees.* *Minor updates to language on ethical, legal, and regulatory norms and standards were made for consistency with paragraph 10.*	
2013 DoH Language: 23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.	**Workgroup Proposal:** 23. The ~~research~~ protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the ~~study~~ **research** begins. This committee must be transparent in its functioning **and** must **have the independence and authority to resist undue influence from the researcher, the sponsor, or others**. ~~and any other undue influence and must be duly qualified.~~ **The committee must have sufficient resources to fulfill its duties, and its members and staff must collectively have adequate education, training, qualifications, and diversity to effectively evaluate each type of research it reviews**. ~~It~~ **The committee must have sufficient familiarity with local circumstances and context, and include at least one member of the general public.** It must take into consideration the **ethical, legal, and regulatory norms and standards** ~~laws and regulations~~ of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research **participants** ~~subjects~~ set forth in this Declaration. **When collaborative research is performed internationally, the research protocol must be approved by research ethics committees in both the sponsoring and host countries.**

	The committee must have the right to monitor**, recommend changes to, withdraw approval for, and suspend** ongoing ~~studies~~ **research. Where monitoring is required,** the researcher must provide ~~monitoring~~ information to the committee **and/or competent data and safety monitoring entity,** especially ~~information~~ about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the ~~study~~ **research**, the researchers must submit a final report to the committee containing a summary of the ~~study's~~ findings and conclusions.
Privacy and Confidentiality	
Paragraph 24	
2013 DoH Language: 24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.	**Workgroup Proposal:** 24. Every precaution must be taken to protect the privacy of research **participants** ~~subjects~~ and the confidentiality of their personal information.
~~**Informed Consent**~~ **Free and Informed Consent**	
Paragraph 25 *The Workgroup proposed adding language here to acknowledge the central role of individual autonomy in the Declaration's protection of research participants.* *The Workgroup proposed consistent use of "free and informed consent" in the Declaration.* *The Workgroup agreed with period two public comments that the term "community leaders" may be unclear, and suggests changing to "community representatives."* *The Workgroup eliminated gendered language.*	

The Workgroup considered period two public comments suggesting the addition of "dignity" to "autonomy." The Workgroup heard additional feedback in Washington that dignity fits better in paragraph 9 than in this paragraph on free and informed consent, so removed its proposed addition here and is focusing on autonomy instead in the first sentence of this paragraph.

2013 DoH Language:	**Workgroup Proposal:**
25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.	25. **Free and informed consent is an essential component of respect for individual autonomy.** Participation by individuals capable of giving informed consent ~~as subjects~~ in medical research must be voluntary**.** Although it may be appropriate to consult family members or community ~~leaders~~ **representatives**, ~~no~~ individual**s** capable of giving informed consent may **not** be enrolled in ~~a~~ research ~~study~~ unless ~~he or she~~ **they** freely agree. ~~s~~

Paragraph 26

In public comment period one, the Workgroup proposed added language to acknowledge increasingly common electronic methods of documenting informed consent. Further public feedback was appreciative of these edits.

The Workgroup received many period one public comments stating that consent information should be tailored to participant "communication needs" and added proposed language to accomplish that goal. The Workgroup also agreed with period two public comments suggesting addition of "in plain language."

The Workgroup deleted "institutional affiliations" because it is already covered by "conflicts of interest." The Workgroup also added to the list of items the participant must be informed of to include the qualifications of the researcher. The Workgroup also recommends the addition of provisions to protect privacy and confidentiality be included in consent given the importance of these risk mitigations required in paragraph 24. The Workgroup made additional changes to the list of items in the informed consent and reordered it for consistency with the list of items in the protocol listed in paragraph 22.

The Workgroup recommended changing "study" to "research" for consistency across the Declaration.

See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other qualified individual" in the third subsection of this paragraph.

2013 DoH Language:	**Workgroup Proposal:**
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding,	26. In medical research involving human ~~subjects~~ **participants** capable of giving informed consent, each potential ~~subject~~ **participant** must be adequately informed **in plain language** of the **aims, methods, anticipated benefits and**

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, post-study provisions and any other relevant aspects of the study. The potential subject must 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 information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study	**potential risks and burdens, qualifications of the researcher, sources of funding, any potential conflicts of interest, provisions to protect privacy and confidentiality, incentives for participants, provisions for treating and/or compensating participants who are harmed as a consequence of participation, and any other relevant aspects of the research.** ~~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, post-study provisions and any other relevant aspects of the study.~~ The potential ~~subject~~ **participant** must be informed of the right to refuse to participate in the ~~study~~ **research** or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information **and communication** needs of individual potential ~~subjects~~ **participants** as well as to the methods used to deliver the information. After ensuring that the potential ~~subject~~ **participant** has understood the information, the physician or another ~~appropriately~~ qualified individual must then seek the potential ~~subject's~~ **participant's** freely given informed consent, ~~preferably in writing~~ **formally documented on paper or electronically.** If the consent cannot be expressed ~~in writing~~ **on paper or electronically,** the non-written consent must be formally ~~documented and witnessed~~ **witnessed and documented**. All medical research ~~subjects~~ **participants** should be given the option of being informed about the general outcome and results of the ~~study~~ **research.**
Paragraph 27 *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other researcher" in this paragraph.* *The Workgroup agreed with a period 2 public comment suggesting deletion of the word "completely" to eliminate redundancy.*	
2013 DoH Language: 27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the	**Workgroup Proposal:** 27. When seeking informed consent for participation in ~~a~~ research ~~study~~ the physician **or other researcher** must be particularly cautious if the potential ~~subject~~ **participant** is in a dependent relationship with the**m** ~~physician~~ or may

physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.	consent under duress. In such situations, the informed consent must be sought by an appropriately qualified individual who is ~~completely~~ independent of this relationship.
Paragraph 28 *In response to regional meeting feedback at the Tokyo meeting, the Workgroup's public comment period one proposal added language about the responsibility of researchers to attempt to honor prior expressed preferences and values of participants when seeking consent from a legally authorized representative.* *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other qualified individual" in this paragraph.* *The Workgroup proposed consistent use of "free and informed consent."* *The Workgroup noted that the second half of the 2013 version of Paragraph 28 listing protections for those incapable of giving informed consent largely recapitulated the special protections for the **particularly vulnerable** as now listed in proposed revisions to Paragraph 20, and then made an additional requirement for minimal risk/burden when there is no likelihood of personal benefit for those incapable of giving consent. So the Workgroup proposed to make that link with new paragraph 20 explicit by noting that those incapable of giving consent are particularly vulnerable and entitled to the three corresponding special protections (as described in paragraph 20). The proposed language then states the additional requirement for minimal risk and minimal burden when research on this population has no likelihood of personal benefit.* *Additional feedback at the regional meeting in Washington helped the Workgroup to improve the language and clearly state that this subgroup (incapable of consent) is entitled to the 3 protections for all of the particularly vulnerable from paragraph 20, plus they also have a requirement for personal benefit, unless there is minimal risk/burden.*	
2013 DoH Language: 28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.	**Workgroup Proposal:** 28. ~~For a potential~~ **In medical** research ~~subject~~ **involving human participants** ~~who is~~ incapable of giving **free and** informed consent, the physician **or other qualified individual** must seek informed consent from the legally authorized representative**, considering preferences and values expressed by the potential participant.** ~~These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be~~

	~~performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.~~ **Those persons incapable of giving free and informed consent are in situations of particular vulnerability and are entitled to the corresponding safeguards. In addition to receiving the protections for the particularly vulnerable, those incapable of giving consent must only be included if the research is likely to either personally benefit them or if it entails only minimal risk and minimal burden.**
Paragraph 29 *In response to regional meeting feedback in Tokyo, the Workgroup's public comment period one proposal added language about the responsibility of researchers to attempt to honor prior expressed preferences and values of participants when seeking consent from a legally authorized representative.* *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other qualified individual" in this paragraph.* *The Workgroup deleted the word "deemed" for consistency with paragraph 28 and for using ethical rather than legislative/regulatory language.*	
2013 DoH Language: 29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.	**Workgroup Proposal:** 29. When a potential research ~~subject~~ **participant** who is ~~deemed~~ incapable of giving **free and** informed consent is able to give assent to decisions about participation in research, the physician **or other qualified individual** must seek that assent in addition to the consent of the legally authorized representative, **considering any preferences and values expressed by the potential participant.** The potential ~~subject's~~ **participant's** dissent should be respected.
Paragraph 30 *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other qualified individual" in the third subsection of this paragraph.* *The Workgroup rephrased the final sentence (on obtaining free and informed consent as soon as possible) for additional clarity.*	

2013 DoH Language: 30. 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 group. In such circumstances the physician must 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 specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or legally authorized representative.	**Workgroup Proposal:** 30. Research involving ~~subjects~~ **participants** 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 group. In such circumstances the physician **or other qualified individual** must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the ~~study~~ **research** may proceed without informed consent provided that the specific reasons for involving ~~subjects~~ **participants** with a condition that renders them unable to give informed consent have been stated in the research protocol and the ~~study~~ **research** has been approved by a research ethics committee. **Free and informed** consent to remain in the research must be obtained as soon as possible from ~~the subject or~~ **a** legally authorized representative **or, if they regain capacity to give consent, from the participant.**
Paragraph 31 *See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other researcher" in this paragraph.* *The Workgroup made an additional change in response to period two public comments suggesting language that withdrawal from research must not adversely affect "the standard of care" provided to the patient.*	
2013 DoH Language: 31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.	**Workgroup Proposal:** 31. The physician **or other researcher** must fully inform ~~the patient~~ **potential participants** which aspects of their care are related to the research. The refusal of a patient to participate in ~~a study~~ **research** or the patient's decision to withdraw from ~~the study~~ **research** must never adversely affect the patient-physician relationship **or provision of the standard of care.**
Paragraph 32 *In public comment period one, the Workgroup responded to feedback especially from the regional meeting in Tel Aviv that the Declaration lacked adequate reference to consent requirements and participant protections for the growing use of personal data stored after trials, especially given the emergence of artificial intelligence, machine learning, collection of genetic data, and risk of re-identification of any de-identified data. The Workgroup*	

proposed a replacement of paragraph 32 to expand beyond biobanks and to cross-reference the WMA Declaration of Taipei (DoT) and highlight its most essential components related to human research.

Many period one public comments welcomed the reference to DoT, while some others did not. The Workgroup recommended including the reference to DoT because of its critical importance to the handling of research participants' data and tissue and because of the explosive growth of large-scale data collection in research. The Workgroup further clarified that this paragraph (in the DoH) is discussing storage of data and material "from research participants" rather than in all health databases (as the DoT more broadly references) or existing electronic health records or non-research registries. The Workgroup agreed with a suggestion to add "secondary" after "foreseeable" in the first sentence to further clarify that the additional informed consent discussed here refers to use beyond the primary study. The Workgroup added "collection" in the second sentence for consistency.

The Workgroup heard additional arguments in favor of and against references to the DoT at the regional meeting in Washington, and is recommending that the DoH retain the new reference because of an ongoing lack of awareness across the research enterprise for the importance of the risks of data collection and the ethical imperative to protect the confidentiality and privacy of research participants. The Workgroup also felt that referencing the DoT was important because it could not adequately recapitulate its important requirements related to research here in the DoH. The WMA recognizes that this ties the DoH and DoT together, but notes that the DoH already also references the Declaration of Geneva and ICoME, so the referencing of other seminal WMA documents is not new to the DoH. The WMA also is committed to updating the DoT to ensure that it remains current and relevant in a rapidly changing landscape of data collection and research.

The Workgroup also heard a comment at the regional meeting in Washington that nearly all "de-identified" data are now essentially re-identifiable and therefore suggesting deletion of the words "or re-identifiable." The Workgroup, however, is concerned about an ongoing lack of awareness of these risks, and desired making a strong statement to the research community about the risks to research participants of re-identifiable data, and voted to keep the reference.

The Workgroup initially had proposed new language reiterating participant rights to withdraw consent for ongoing data storage where possible, while acknowledging that there are circumstances in which material or data cannot be legally or practically withdrawn. However, after the Workgroup reviewed period 2 public comments, it recommended instead that the DoH reference data governance principles in the DoT and eliminate specific mention here of rights to have data withdrawn from databases.

The Workgroup recommended retaining a last sentence in 2013 language specifically calling out the need for research ethics committee review and approval when it is impossible or impracticable to obtain consent for unforeseen secondary research on stored data or material.

See the description above paragraph 9 for a discussion of the Workgroup's rationale for the use of "physician or other qualified individuals" in this paragraph.

2013 DoH Language:	**Workgroup Proposal:**
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.	32. ~~For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.~~ **Physicians or other qualified individuals must obtain free and informed consent from research participants for the collection, processing, storage, and foreseeable secondary use of biological material and identifiable or re-identifiable data. Any collection and storage of data or biological material from research participants for multiple and indefinite uses should be consistent with requirements set forth in the WMA Declaration of Taipei, including the rights of individuals and the principles of governance. A research ethics committee must approve the establishment and monitor ongoing use of such databases and biobanks.** **Where consent is impossible or impracticable to obtain, secondary research on stored data or biological material may be done only after consideration and approval of a research ethics committee.**

Use of Placebo

Paragraph 33

The Workgroup undertook an in-depth review following the regional meeting in São Paolo with attendees from 10 Latin American countries and representatives from Confederación Médica Latinoamericana y del Caribe (CONFEMEL) and the Pan American Health Organization. This review and related discussions continued across subsequent meetings with CONFEMEL members at other meetings in the region.

The Workgroup proposed in public comment period one to clarify that the first exception when there is "no proven intervention" should refer instead to when there is no "safe and effective" intervention. This stemmed from the reality that researchers would not want to subject participants to a highly toxic but proven intervention as a comparator arm. However, at the urging of some public commenters including CONFEMEL members who raised concern about potential misinterpretation, the Workgroup subsequently deleted the proposed addition of "safe and effective" to mitigate risk of abuse.

The Workgroup also clarified that there can sometimes be more than one proven intervention with similar efficacy and safety (with the change to "best proven one(s)." *Based on a suggestion from CONFEMEL, the Workgroup clarified that interventions can be considered inferior to the best proven one(s) not only because of low efficacy, but also because of unacceptable side-effects or risk profiles (by removing the words "less effective")* *The Workgroup agreed with period two public comments suggesting changing "Where" to "If."* *The Workgroup agreed with period two public comments suggesting changing "patients" to "participants" in recognition that some healthy volunteers may be in studies that could involve placebos.*	
2013 DoH Language: 33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks 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.	**Workgroup Proposal:** 33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: ~~Where~~ **If** no proven intervention exists, the use of placebo, or no intervention, is acceptable; or ~~Where~~ **If** for compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one**(s)**, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention**;** and the ~~patients~~ **participants** who receive any intervention ~~less effective~~ **other** than the best proven one**(s)**, placebo, or no intervention will not be subject to additional risks 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.

Post-Trial Provisions	
Paragraph 34 *Because of concerns raised at a topical meeting on research in low-resource settings at the Vatican, the Workgroup proposed strengthened language to state that post-trial provisions must be arranged for study participants who need access to the trial intervention. However, the new language also clarifies that while the sponsor and researcher have responsibilities for arranging these provisions, healthcare systems and governments are also sometimes the providers of post-trial provisions. New language states that the provisions "must" be arranged but permits exceptions if approved by an ethics committee.* *The Workgroup initially proposed changing "beneficial" to "safe and effective," but heard feedback at the regional meeting in Washington about "safe and effective" being too similar to regulatory language that could be misconstrued, and is now instead recommending "beneficial and reasonably safe."*	
2013 DoH Language: 34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.	**Workgroup Proposal:** 34. In advance of a clinical trial, ~~sponsors, researchers and host country governments should make~~ **post-trial** provisions ~~for post-trial access~~ **must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or governments** for all participants who still need an intervention identified as beneficial **and reasonably safe** in the trial. **Exceptions to this requirement must be approved by a research ethics committee.** ~~This~~ **Specific** information **about post-trial provisions** must ~~also~~ be disclosed to participants **as part of** ~~during the~~ informed consent. ~~process~~
Research Registration, Publication, and Dissemination of Results	
Paragraph 35	
2013 DoH Language: 35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.	**Workgroup Proposal:** 35. ~~Every~~ M**edical** research ~~study~~ involving human **participants** ~~subjects~~ must be registered in a publicly accessible database before recruitment of the first **participant** ~~subject~~.

Paragraph 36 *The Workgroup agreed with feedback that making results publicly available in a timely fashion is an ethical responsibility of researchers. The Workgroup felt that "timeliness" fit better in the second rather than in the first sentence, as editors and publishers referenced in the first sentence may have broader ethical responsibilities to prioritize certain research for quicker publication over other research, or to reject manuscripts that fail to meet certain criteria.*	
2013 DoH Language: 36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.	**Workgroup Proposal:** 36. Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human **participants** ~~subjects~~ and are accountable for the **timeliness**, completeness, and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations**,** and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
Unproven Interventions in Clinical Practice	
Paragraph 37 *The Workgroup proposes a rewritten paragraph 37 because of substantial feedback at multiple regional and topical meetings about the paragraph's misuse during the COVID-19 pandemic. The phrase "may use" from the previous version was inappropriately relied upon to justify use of therapies proven **in**effective – that prior phrasing was misinterpreted to imply a right. Because this Declaration is focused on ethical principles for medical research (and not clinical care more broadly), the Workgroup proposal now focuses on the intersection of the use of unproven interventions and the research enterprise – namely, it emphasizes that unproven intervention provisions (sometimes known as compassionate use) should not be exploited to circumvent the DoH. The new language acknowledges situations in which unproven interventions are sometimes tried, but to better align with the purposes of the DoH, it now focuses on the research implications of these uses.*	

2013 DoH Language:	**Workgroup Proposal:**
37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.	37.~~In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.~~ **When an unproven intervention is utilized in an attempt to restore health or alleviate suffering for an individual patient because approved options are inadequate or ineffective and enrollment in a clinical trial is not possible, it should subsequently be made the object of research designed to evaluate safety and efficacy. Physicians participating in such interventions must first seek expert advice, weigh possible risks, burdens, and benefits, and obtain informed consent. They must also record and share data when appropriate and avoid compromising clinical trials. These interventions must never be undertaken to circumvent the protections for research participants set forth in this Declaration.**