MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

June 24, 2024

Declaration of Helsinki Public Comment Period Two

COMMENTING ORGANIZATION (if applicable): The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard ("MRCT Center")

COMMENT PREPARER (name and title): Barbara E. Bierer, MD

Please indicate whether you are commenting on behalf of the organization identified above☒ or yourself ☐. Check one box.

Comments not submitted in the proper format will be returned for correction. COMMENTS RECEIVED AFTER THE JUNE 24 DEADLINE WILL NOT BE CONSIDERED.

FORMAT AND INSTRUCTIONS

This document includes the current 2013 Declaration of Helsinki (DoH) language in the first column, and the WMA DoH Workgroup's suggested edits, if any, in the second column. The workgroup's rationale for any proposed changes in each paragraph appears in *italics*. The workgroup's changes are indicated with **underscoring** and ~~**strikethrough**~~. The "Workgroup Proposal" reflects feedback received during public comment period one (held from January-February 2024) and all regional and topical meetings to date.

To leave a comment:

1- If proposing language edits, copy and paste the "Workgroup Proposal" from the righthand column in the space provided under the paragraph you wish to comment on. Indicate suggested **additions** with **bold yellow highlighted language**. Indicate suggested ~~deletions~~ with ~~yellow highlighted strikethrough language~~. **DO NOT USE TRACK CHANGES.**
2- Place any commentary, rationale, or explanations in [brackets]. **See example below.**

Comments not submitted in the proper format will be returned for correction. COMMENTS RECEIVED AFTER THE JUNE 24 DEADLINE WILL NOT BE CONSIDERED.

Example 2013 DoH Language:	**Example Workgroup Proposal:**
The brown dog went fast.	The ~~brown~~ dog went **really** fast.

Example Comment:

The ~~brown~~ dog went ~~really~~ fast **and completed the race**. [My medical association does not think the dog went "really" fast. We do think it is important to clarify that the dog completed the race.]

Preamble

Paragraph 1
The workgroup proposes replacing "subjects" with "participants" throughout the DoH out of respect for the rights, agency, and importance of those individuals. (See e.g., Workgroup Proposal paragraphs 1, 10, 12, 14, etc.)

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 on identifiable human material and research 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 on identifiable human material and research 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.

Comment:
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 on identifiable human material and research and data. **These principles and the term "participant" also apply to instances where consent has been waived or is not necessary.**

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.

[We appreciate the agency embodied by use of the word "participants" in lieu of "subjects." Our only concern is whether the term encompasses the full spectrum of clinical research. For example, some research may use identifiable data or biospecimens for which consent has been waived

or is not necessary. For these reasons, individuals whose clinical data or biospecimens are the subject of research may not even be aware of the trial that aims to study them. The minor edit we suggest assuages this concern.]	
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 the research. The proposed language also recognized that participants in medical research include both patients and healthy volunteers.* *Many period one public commenters supported paragraph 2 applying to **all** researchers. Commenters also pointed out 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 have been made to reflect those points. Some commenters suggested reordering the phrases in the sentence for clarity, which the workgroup proposes below. The workgroup also proposes adding "respect" to "protection" to emphasize the agency of participants.*	
2013 DoH Language: 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.	**Workgroup Proposal:** ~~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 they are fundamental to respect for and protection of all research participants, whether patients or healthy volunteers.**
Comment:	
General Principles	
Paragraph 3	

No proposed changes.	
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."	**Workgroup Proposal:** 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." [**No proposed changes.**]
Comment:	
Paragraph 4 *No proposed changes.*	
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.	**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.**]
Comment: 4. It is the duty of the physician to promote and safeguard the health, well-being, and rights of patients **and healthy volunteers**, including those who ~~are involved~~ **participate** in medical research. The ~~**physician's**~~ knowledge **and conscience of the physician and other qualified researchers should be** ~~are~~ dedicated to the fulfilment of this duty. [We believe this minor change more consistently reflects the proposal to adopt the term "trial participants" over "subjects" and is a better indicator of participants' agency, and should include mention of healthy volunteers. In addition, the duty extends to other qualified researchers]	
Paragraph 5	

*The workgroup proposes moving the last sentence of the 2013 paragraph 6 about continuous evaluation of best proven interventions up to the end of paragraph 5. Within the sentence, the workgroup agreed with public comment suggestions to change "must" to "should" given that researchers cannot continuously evaluate **all** of the hundreds of thousands of medical therapies.*	
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 proven interventions ~~must~~ should be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.** [Moved up from paragraph 6 (2013).]
Comment:	
Paragraph 6 *The workgroup received many suggestions during public comment period one to move the 2013 paragraph 7 before the 2013 paragraphs 6 and 8 for continuity. The 2013 paragraph 7 now appears here as the proposed paragraph 6 (i.e., reordered to 7, 6, 8).* *Based on feedback heard at regional and topical meetings, the workgroup also proposes a new aspirational sentence about global justice, which acknowledges inequity and urges researchers to carefully consider where and with whom research is carried out.* *New language about the importance of meaningful engagement with potential participants and their communities is also proposed by the workgroup in response to comments at regional meetings about the importance 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 is subject to ethical standards that promote and ensure respect for all human ~~subjects~~ **participants** and protect their health and rights. **Since it takes place in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens of medical research are distributed.** **Meaningful engagement with potential and enrolled participants and their communities should occur before, during, and following medical research involving human participants. Researchers should empower potential and enrolled participants and their communities to share their priorities and values; participate in study design, implementation, and other relevant activities; and engage in understanding and disseminating results.**

Comment:
~~7.~~**6.** Medical research is subject to ethical standards that promote and ensure respect for all human ~~subjects~~ **participants** and protect their health and rights.

Since it takes place in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens of medical research are distributed.

Meaningful engagement with potential and enrolled participants and their communities should occur before, during, and following medical research involving human participants. Researchers and others involved in clinical research should empower potential and/or enrolled participants and their communities to share their priorities and values; participate in study design, implementation, and other relevant activities; and engage in understanding and disseminating results.

[We believe the minor edits we suggest here promote clarity in the interpretation of this paragraph. Enrolled participants likely cannot participate in study design, for example. In addition, it is not only researchers but also institutions, ethics committees and others who are or should be engaged with the participants and communities.]

Paragraph 7

In public comment period one, based upon feedback from regional meetings, the workgroup proposed specific mention of "social value," including individual and public health as additional primary purposes of conducting medical research.

The workgroup received many public comments expressing concern with the vagueness of the proposed term social value. The workgroup now proposes edits below based on public suggestions to reference advancing individual and public health without using the term social value.

The workgroup also received many suggestions during public comment period one to move the 2013 paragraphs 6 and 8 together given their relationship to each other, so they are combined and harmonized here as proposed paragraph 7.

The workgroup also proposes 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:	**Workgroup Proposal:**
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.	~~6.~~**7**. The primary purpose**s** of medical research involving human ~~subjects~~ **participants** ~~is~~ **are** 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.~~ [Sentence moved up to paragraph 5.] ~~8.While the primary~~ **These purposes** ~~of medical research is to generate new knowledge, this goal~~ can never take precedence over the rights and interests of individual research **participants** ~~subjects~~.

Comment:

~~6.~~**7**. The primary purpose**s** of medical research involving human ~~subjects~~ **participants** ~~is~~ **are** 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.~~ [Sentence moved up to paragraph 5.]

~~8.While the primary~~ **These purposes** ~~of medical research is to generate new knowledge, this goal~~ ~~can~~ **must** never take precedence over the rights and interests of individual research **participants** ~~subjects~~. [We believe this minor edit takes an equally strong stance against the proscribed action while simultaneously implicitly acknowledging that the proscribed action can indeed happen.]

Paragraph 8 *The workgroup proposes this new paragraph based on recommendations at regional meetings 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.**
Comment: **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, regardless of their severity or duration.**	
Paragraph 9 *Consistent with proposed updated paragraph 2 stating that the DoH principles should be upheld by all involved in medical research, the workgroup proposes incorporating public comments suggesting use of "or other qualified researchers" rather than "health care professionals."*	
2013 DoH Language: 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.	**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 **participants** ~~subjects~~. The responsibility for the protection of research **participants** ~~subjects~~ must always rest with the physician or other **qualified researchers** ~~health care professionals~~ and never with the research **participants** ~~subjects~~, even though they have given consent.

Comment: 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 **participants** ~~subjects~~ **and the confidentiality of their personal information**. The responsibility for the protection of research **participants** ~~subjects~~ must always rest with the physician or other **qualified researchers** ~~health care professionals~~ and never with the research **participants** ~~subjects~~, even though they have given consent **(or assent, in the case of vulnerable participants incapable of providing consent)**. [The minor edits we recommend here clarify that the "life, health, dignity…" etc. to be protected belongs to the participants and not to their "confidential information." Additionally, because the revisions proposed throughout the document aim to include vulnerable participants and because certain vulnerable participants may be capable of expressing assent in ways that do not meet the threshold for adequate informed consent, the parenthetical we propose to add captures this circumstance in the context of Paragraph 9.]	
Paragraph 10 *Consistent with proposed updated paragraph 2 stating that the DoH principles should be upheld by all involved in medical research, the workgroup proposes incorporating public comments suggesting the addition of "and other qualified researchers" into this guidance.* *This paragraph has also been updated to be consistent with the proposed edits to paragraph 23, which require host country ethics committee approval for international research.*	
2013 DoH Language: 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.	**Workgroup Proposal:** 10. Physicians **and other qualified researchers** must consider ~~the~~ ethical, legal and regulatory norms and standards for research involving human **participants** ~~subjects~~ in their own countries (**and in host countries for international research).** ~~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.
Comment:	

10. Physicians **and other qualified researchers** must consider ~~the~~ ethical, legal and regulatory norms and standards for research involving human **participants** ~~subjects~~ in their own countries (**and in host countries for international research).** ~~as well as applicable international norms and standards.~~ **While local legal and regulatory norms and standards may impose additional requirements, n**~~N~~o 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.

[The minor edits suggested here seek to clarify that the principles set forth in the Declaration represent a floor, not a ceiling, for the minimum conduct of clinical researchers.]

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 International Code of Medical Ethics.

Many public comments supported additional emphasis on the environment but advised deletion of "possible" in the 2013 version and expressed concern about vagueness of "promotes sustainability" that was proposed in public comment period one.

The workgroup deleted "possible" and withdrew "and promotes sustainability," and proposes adding "designed and" and "avoids or" to strengthen this paragraph.

2013 DoH Language:	**Workgroup Proposal:**
11. Medical research should be conducted in a manner that minimises possible harm to the environment.	11. Medical research should be **designed and** conducted in a manner that **avoids or** minimises ~~possible~~ harm to the environment.

Comment:

Paragraph 12

2013 DoH Language:	**Workgroup Proposal:**

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 competent and appropriately qualified physician or other health care professional.	12. Medical research involving human **participants** ~~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 competent and appropriately qualified physician or other health care professional.

Comment:
12. Medical research involving human **participants** ~~subjects~~ must be conducted only by individuals with the appropriate ethics, **medical,** and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

[Medical education, training, and qualifications are necessary in addition to scientific and ethical considerations.]

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**.]

Comment:
13. Groups that are underrepresented in medical research should be provided ~~appropriate~~ **equitable** ~~**access to the**~~ **opportunity to be offered** participation in research. **To the extent practicable, the trial population should be representative of the prospective patient population; eligibility criteria that exclude groups or individuals should be explicitly justified based on safety, medical, or ethical reasons.**

[We believe the proposed addition better reflects the intent of Paragraph 13 and helps to connect access to clinical research with representation while still acknowledging that there is no right to access a trial, but there is a right to be offered an equitable opportunity to be offered participation. Exclusion should be based on safety, medical, or ethical reasons to prevent discrimination.]

Paragraph 14	
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~~
Comment: 14. Physicians who combine medical research with medical care should ~~involve~~ **provide** their patients **with opportunities to participate** 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~~ [We believe the change recommended here better promotes the agency of trial participants.]	
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.
Comment:	

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~~.
Comment:	
Paragraph 17	
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. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.	**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.

Comment:
17. All medical research involving human **participants** ~~subjects~~, **their clinical data or biospecimens** must be preceded by careful assessment of predictable risks and burdens to the individuals and groups ~~involved~~ **who participate** 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.

[Once again, we believe referencing participation in clinical trials in active terms more completely fosters participant agency and extends the protections considered in this paragraph to participants' data and biospecimens.]

Paragraph 18
Consistent with the proposed edits to paragraph 2 that state the DoH principles should be upheld by all involved in medical research, the workgroup proposes incorporating public comments suggesting use of "and other qualified researchers."

2013 DoH Language:	**Workgroup Proposal:**
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.	18. Physicians **and other qualified researchers** may not be involved in a research study involving human **participants** ~~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 **and other qualified researchers** must assess whether to continue, modify or immediately stop the study.

Comment:
18. Physicians **and other qualified researchers** may not be involved in a research study involving human **participants** ~~subjects~~ unless they are confident that the risks have been adequately assessed and can be satisfactorily **eliminated, mitigated, or** managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians **and other qualified researchers** must assess whether to continue, modify or immediately stop the study.

[We distinguish between managing risks and mitigating or eliminating them.]

~~Vulnerable Groups and Individuals~~ Individual, Group, and Community Vulnerability

The workgroup proposes amending this section title to use the word "vulnerability" rather than "vulnerable" to address feedback from regional and topical meetings that vulnerability may be contextual and dynamic.

Paragraph 19

Based on feedback from regional and topical meetings, the workgroup proposes substantial edits to paragraphs 19 and 20 to update discussions about vulnerability so that groups experiencing vulnerability can, when appropriate, benefit from responsible inclusion in research, but also receive specifically considered protections.

The first sentence of replacement paragraph 19 addresses the contextual and dynamic nature of vulnerability and maintains language about a greater risk of incurring harm. The second sentence adds a new acknowledgement that exclusion from research can exacerbate vulnerability and disparities. The third sentence reinforces the need for specifically considered protections using the language "responsible inclusion," which was offered during a topical meeting.

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 experience more vulnerability as research participants due to factors that may be fixed or contextual and dynamic, and thus are at greater risk of incurring harm. When such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their vulnerability and disparities. In order to be responsibly included in research, those experiencing vulnerability should receive specifically considered protections.**

Comment:

~~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 experience more vulnerability as research participants due to factors that may be fixed or contextual and dynamic, and thus are at greater risk of incurring harm. When such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their vulnerability and disparities. In order to be responsibly included in research, those experiencing vulnerability should receive specifically considered protections.**~~

19. Some individuals, groups, and communities experience more vulnerability as research participants due to distinctive health and social/environmental conditions that result from factors that may be fixed, contextual, and/or dynamic, and are thus at greater risk of incurring harm. However, excluding such individuals, groups, and/or communities from participating in medical research may potentially perpetuate or exacerbate their vulnerability and the disparities they experience as a result. Therefore, any exclusion of such populations from participation in a particular trial must be clearly and explicitly justified for safety, medical, or ethical reasons in the trial protocol. Provided that vulnerable individuals, groups, and/or communities are able to provide informed consent, with accommodations if needed, physicians and other qualified researchers should provide accommodations and additional protections such that they can participate safely in the clinical research process.

[These edits we suggest here recognize the valuable contributions to medical and scientific knowledge that participants from vulnerable communities may provide, should they choose to participate in the research process. Knowing that different populations may respond differently to interventions, barriers to access should be removed whenever possible. We recognize too that, on many occasions, the distinctive health needs that may render an individual, group, or community vulnerable – e.g., limited mobility – would not preclude a vulnerable population from receiving a particular intervention post-approval. We therefore contend that inclusion-by-design of vulnerable populations yields higher quality data that better represent the intended patient population. We believe the edits we recommend here embody the spirit of WMA's proposed text while providing more granularity to clinical research stakeholders regarding how best to engage and protect vulnerable populations through research.]

Paragraph 20

As noted above, the workgroup proposes substantial edits to paragraphs 19 and 20 to update discussions of vulnerability so that groups experiencing vulnerability can, when appropriate, benefit from responsible inclusion in research but also receive specifically considered protections.

*While proposed revisions to paragraph 19 add new language about balancing the risks of excluding those experiencing vulnerability from medical research, paragraph 20 retains three important protections for some **particularly** vulnerable individuals, groups, and communities. It also inserts consideration of whether carrying out research in non-vulnerable groups would exacerbate disparities for vulnerable groups (for example, our ongoing deficit of information about drug efficacy and risks in children).*

2013 DoH Language: 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.	**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 some particularly vulnerable individuals, groups, or communities is only justified if it is responsive to their health needs or priorities; they stand to benefit from the resulting knowledge, practices, or interventions; and the research cannot be carried out in a non-vulnerable group, unless excluding them would perpetuate or exacerbate their vulnerability or disparities.**

Comment:

~~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 some particularly vulnerable individuals, groups, or communities is only justified if it is responsive to their health needs or priorities; they stand to benefit from the resulting knowledge, practices, or interventions; and the research cannot be carried out in a non-vulnerable group, unless excluding them would perpetuate or exacerbate their vulnerability or disparities.**~~

20. Some individuals, groups, and communities experience vulnerability due to distinctive health and social/environmental conditions; their inclusion in clinical research may be justified when the research is responsive to their health needs and/or their priorities/values; they stand to benefit from the resulting knowledge, practices, or interventions and/or by a sense of value for contributing to research that may help others; they are able to provide adequate informed consent, with accommodations if needed; and excluding them would potentially perpetuate or exacerbate their vulnerability or disparities. The study protocol should describe which vulnerable individuals, groups, and/or communities may be at risk of exploitation and/or greater harm and describe how the study will seek to accommodate their needs whenever practicable and empower them to participate safely in the clinical research process.

[The revisions we recommend here first eliminate the subjectivity inherent in the "particularly vulnerable" designation relative to "vulnerable" and the corresponding practical questions that would abound regarding who would make such a determination. Instead, the revisions here, like those above in Paragraph 19, presuppose the distinctive health needs of all vulnerable populations and the increased risks of harm and/or exploitation they may face.]

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).

The workgroup now proposes incorporating suggestions from public comments to add "and execution" and to change "information" to "knowledge." The workgroup also added specific mention of "research waste" based upon public feedback about the harms to participants in studies that have no chance of advancing health due to poor design. Commenters also noted the word "medical" was missing after public comment period one and felt "rigorous" was important to add after "sound."

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.

Comment:

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 **to inform human participant** research must be respected.

[The edit proposed here aims to clarify the scope of the Declaration.]

Paragraph 22
Note: Updated language on post-trial provisions is fully addressed in paragraph 34. Changes to paragraph 22 are proposed for harmonization.

2013 DoH Language:	**Workgroup Proposal:**
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.	22. The design and performance of each 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 funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for **participants** ~~subjects~~ and information regarding provisions for treating and/or compensating **participants** ~~subjects~~ who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe ~~appropriate~~ **any post-trial provisions.** ~~arrangements for post-trial provisions.~~

Comment:
22. The design and performance of each 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 funding, sponsors, and institutional affiliations; potential conflicts of interest; **reimbursement for expenses and compensation for time and burden of participants and their caregivers;** incentives for **participants**

~~subjects~~; and information regarding provisions for treating and/or compensating **participants** ~~subjects~~ who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe ~~appropriate~~ **any post-trial provisions.** ~~arrangements for post-trial provisions.~~

[The edit proposed here acknowledges that reimbursement for expenses and compensation for the time and burden of participation for both the participant and necessary attendant should be detailed in the protocol. Participants should not be worse off at the end of a trial for having participated.]

Research Ethics Committees

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 also added specificity to their qualifications.

In response to public comments, the workgroup now proposes broadening the requirements for ethics committees to include adequate education, training, and qualifications, mirroring the requirements for researchers in paragraph 12. The workgroup also incorporated a suggestion from commenters to include "diversity." The workgroup proposes adding language about committee understanding of local context and strengthening the undue influence section.

The workgroup also proposes new text based on feedback at regional meetings about requiring international research be approved in host countries (not only sponsor countries).

In the final paragraph, the workgroup responded to public comments suggesting additional language that committees must be able to change or suspend studies and that committees can and do utilize external monitoring entities.

Paragraph 23

2013 DoH Language:	**Workgroup Proposal:**
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	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.	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 must have sufficient familiarity with local circumstances and context.** 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 **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 ongoing studies, **recommend changes, withdraw approval, and suspend ongoing 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, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Comment:
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 **and** must **have the independence and authority to resist undue influence from the researcher, the sponsor, government entities, 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 must have sufficient familiarity with local circumstances and context. 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 **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 ongoing studies, **recommend changes, withdraw approval, and suspend ongoing 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, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

[In many circumstances, the Workgroup's proposed language requiring ethical review in the "sponsoring country" would not be practicable. Often, ethical review boards *will not* review a study or protocol unless the study proposes to enroll participants in the region/country where the ethics review board operates. Our proposed revisions here seek to capture the spirit underpinning the Workgroup's proposed language while filtering it through the lens of its downstream application. We also recommend an additional, standalone paragraph on ethical review of multi-regional clinical trials at the end of this document.]

Privacy and Confidentiality

Paragraph 24

2013 DoH Language:	**Workgroup Proposal:**
24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.	24. Every precaution must be taken to protect the privacy of research **participants** ~~subjects~~ and the confidentiality of their personal information.

Comment:
24. Every precaution must be taken to protect the privacy of research **participants** ~~subjects~~ and the confidentiality of their personal information **and to comply with applicable privacy laws in every jurisdiction where the trial will be conducted**.

Paragraph 25
The workgroup proposes adding language here to acknowledge the central role of individual autonomy in the DoH's protection of research participants. Gendered language was also replaced.

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. **Informed consent is an essential component of respect for individual autonomy.** Participation by individuals capable of giving informed consent as **participants** ~~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~~ **they** freely agree~~s~~.

Comment:
25. **Informed consent is an essential component of respect for individual autonomy.** Participation by individuals capable of giving informed consent **to participate** ~~as **participants**~~ ~~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~~ **they** freely agree~~s~~. **No individual capable of giving autonomous informed consent may be enrolled without it, and special considerations should be made to present information in age-appropriate ways to minor participants capable of communicating their assent to participate in research.**

[Clinical researchers who conduct trials in paediatric populations rely on the principles set forth in this Declaration and should find specific guidance herein. Specifically, paediatriac trial participants are generally not considered to have the capacity to provide informed consent. However, paediatric patients may nevertheless express their wishes to/not to participate in research – either to their legally authorised representative or directly to the clinical researcher. Though a paediatric participant's assent alone is not sufficient to enroll them in a clinical study, those studies seeking to enroll paediatric participants should dedicate substantial focus to ensuring prospective participants understand the studies for which they are being considered and should place great weight on a paediatric patient's expressed desire *not* to participate in a study.]

Paragraph 26
In public comment period one, the workgroup proposed added language to acknowledge increasingly common electronic methods of documenting informed consent.

The workgroup subsequently received many public comments that consent information should be tailored to participant communication needs and added proposed language to accomplish that goal. The workgroup proposes other clarifying and harmonizing changes.

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, 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	26. In medical research involving human ~~subjects~~ **participants** capable of giving informed consent, each potential ~~subject~~ **participant** 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~~ **burdens** it may entail, post-**trial** ~~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 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 **researcher** ~~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.

Comment:
26. In medical research involving human ~~subjects~~ **participants** capable of giving informed consent, each potential ~~subject~~ **participant** 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~~ **burdens** it may entail, post-**trial** ~~study~~ provisions and any other relevant aspects of the study. **This information should be frank, understandable, and in the preferred language of the prospective participant. Researchers are expected to provide reasonable accommodations for prospective participants who request or need them.**

The potential ~~subject~~ **participant** 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 **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 **researcher** ~~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~~ **clear information regarding whether and how they will be** informed about the general outcome and results of the study **or whether they have the option to request to receive such information**.

[The recommended edits here advance the inclusive motivation behind many of the other proposed revisions to the Declaration by insisting that the informed consent language be understandable to non-sophisticated stakeholders and accessible to those with disabilities not relevant to the study in question.]

Paragraph 27
Consistent with the proposed edits to paragraph 2 that state the DoH principles should be upheld by all involved in medical research, the workgroup incorporated public comments suggesting use of "or other qualified researcher."

2013 DoH Language:	**Workgroup Proposal:**

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 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.	27. When seeking informed consent for participation in a research study the physician **or other qualified researcher** must be particularly cautious if the potential ~~subject~~ **participant** is in a dependent relationship with the**m** ~~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.
Comment:	
Paragraph 28 *In response to regional meeting feedback, 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.* *Consistent with the proposed edits to paragraph 2 that state the DoH principles should be upheld by all involved in medical research, the workgroup incorporated public comments suggesting use of "or other qualified researcher."* *The subject of the second sentence was clarified in response to public comments.*	
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 research ~~subject~~ **participant** who is incapable of giving informed consent, the physician **or other qualified researcher** must seek informed consent from the legally authorised representative**, considering any preferences and values previously expressed by the potential participant.** ~~These individuals~~ **Those unable to provide consent** 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~~ **participant**, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

Comment: ~~28. For a potential research subject **participant** who is incapable of giving informed consent, the physician **or other qualified researcher** must seek informed consent from the legally authorised representative, **considering any preferences and values previously expressed by the potential participant.** These individuals **Those unable to provide consent** 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 **participant**, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.~~ **28. It may be appropriate to include research participants who are incapable of giving explicit informed consent on their own, despite accommodations and/or the presence of a support person. Such occasions must be justified in the study protocol and subjected to ethical review. When seeking to enroll a participant incapable of providing explicit consent, the physician or other qualified researcher must seek informed consent from the legally authorised representative and consider any preferences and values previously expressed by the potential participant that the researcher(s) and/or legally authorised representative reasonably know. A study employing alternative methods of consent, such as deferred consent or community consent, must be justified in the study protocol and subjected to ethical review. Those unable to provide explicit informed consent should 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 participant, the research cannot instead be performed with persons capable of providing explicit informed consent, and the research entails only minimal risk and minimal burden.** [The revisions recommended here correct the omission of alternative methods of ethically obtaining consent to enroll participants in a study. We also acknowledge that a researcher and/or legally authorised representative may not always be reasonably expected to know the preferences of a particular individual but still commit the researcher to honoring those preferences when they are known.]	
Paragraph 29 *In response to regional meeting feedback, 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.* *Consistent with the proposed edits to paragraph 2 that state the DoH principles should be upheld by all involved in medical research, the workgroup incorporated public comments suggesting use of "or other qualified researcher."*	
2013 DoH Language:	**Workgroup Proposal:**

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.	29. When a potential research ~~subject~~ **participant** who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician **or other qualified researcher** 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.
Comment:	
Paragraph 30 *Consistent with the proposed edits to paragraph 2 that state the DoH principles should be upheld by all involved in medical research, the workgroup incorporated public comments suggesting use of "or other qualified researcher."*	
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 researcher** 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~~ **participants** 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~~ **participant** or legally authorized representative.

Comment:
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 **or the individual's preferences have been clearly expressed to their legally authorised representative**. In such circumstances the physician **or other qualified researcher** must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, **or in settings of life-saving potential,** the study may proceed without informed consent ~~provided that~~ **only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group and** 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 has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the ~~subject~~ **participant** or legally authorized representative.

[We believe that circumstances exist wherein a prospective participant who is presently incapable of providing informed consent may be ethically enrolled in studies unrelated to the cause of their lack of capacity – e.g., if an unconscious individual with cancer whose unconsciousness is unrelated to their cancer had previously expressed a preference to their legally authorised representative to participate in cancer research.]

Paragraph 31
Consistent with the proposed edits to paragraph 2 that state the DoH principles should be upheld by all involved in medical research, the workgroup incorporated public comments suggesting use of "or other qualified researcher."

2013 DoH Language:	**Workgroup Proposal:**
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.	31. The physician **or other qualified researcher** 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.

Comment:

Paragraph 32

In public comment period one, the workgroup responded to regional meeting feedback that the DoH 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 de-identified data. The workgroup proposed a replacement of paragraph 32 to expand beyond biobanks and to cross-reference the Declaration of Taipei (DoT) and highlight its most essential components related to human research.

Many public comments welcomed the reference to DoT, while some others did not. The workgroup recommends 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 changing "must" to "should" in the section about withdrawal of consent to recognize some international variation. 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 phrase "where possible" is intended to acknowledge that there are circumstances in which material or data cannot be legally or practically withdrawn.

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 researchers must obtain informed consent from research participants for the collection, 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 Declaration of Taipei, including the right of individuals to alter consent at any time or have material or data withdrawn from**

	databases or biobanks, where possible. A research ethics committee must approve the establishment and monitor ongoing use of such databases and biobanks. In exceptional situations where consent is impossible or impracticable to obtain, research on stored data or biological material may be done only after consideration and approval of a research ethics committee.

Comment:

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 researchers must obtain informed consent from research participants (or the assent of a paediatric participant and the informed consent of their legally authorised representative) for the collection, 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 Declaration of Taipei, including the right of individuals to alter consent at any time or have material or data withdrawn from databases or biobanks, where possible. A research ethics committee must approve the establishment and monitor the conduct of and ~~ongoing~~ new proposed uses of such databases and biobanks. In exceptional situations where consent is impossible or impracticable to obtain, research on stored data or biological material may be done only after consideration and approval of a research ethics committee.

[Our suggestions here seek to be more explicit in the inclusion of paediatric trial participants and in the specific requirements that coincide therewith. Additionally, we worry that requiring "ongoing" use of a biobank by an ethics committee may not be practicable and instead recommend language requiring ethical review of each new study proposing to use the biobank.]

Paragraph 33

The workgroup undertook an in-depth review following the Latin American Regional Meeting with attendees from 10 Latin American countries and representatives from Confederación Médica Latinoamericana y del Caribe (CONFEMEL) and the Pan American Health Organization. The workgroup proposed in public comment period one to clarify that the first exception when there is "no proven intervention" means a "safe and effective" intervention. The workgroup also clarified that there can sometimes be more than one proven intervention with similar efficacy and safety.

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.

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.

2013 DoH Language:	**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 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.	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 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 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.

Comment:

Paragraph 34

Because of concerns raised at a topical meeting on research in low-resource settings, the workgroup proposes 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 host country governments are

also sometimes the providers of them. New language states that the provisions "must" be arranged for but permits exceptions if approved by an ethics committee.

2013 DoH Language:	**Workgroup Proposal:**
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.	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 host country governments** for all participants who still need an intervention identified as **safe and effective** ~~beneficial~~ in the trial. **Exceptions to these provisions must be approved by a research ethics committee.** ~~This~~ **Specific** information **about post-trial provisions** must ~~also~~ be disclosed to participants during ~~the~~ informed consent ~~process~~.

Comment:

~~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 host country governments~~** ~~for all participants who still need an intervention identified as~~ **~~safe and effective~~** ~~beneficial in the trial.~~ **~~Exceptions to these provisions must be approved by a research ethics committee.~~** ~~This~~ **~~Specific~~** ~~information~~ **~~about post-trial provisions~~** ~~must also be disclosed to participants during the informed consent process.~~

34. In advance of a clinical trial, sponsors, researchers, healthcare systems, and host country governments should consider and arrange post-trial provisions for all participants who still need an investigational intervention identified as safe and effective in the course of the trial. In addition to assessing whether the intervention is safe and effective, considerations to provide post-trial provisions should include the severity of the disease, medical need, availability of alternative interventions for the study population, research viability, and local laws and regulations. Exceptions to these provisions must be justified in the trial protocol. Specific information about post-trial provisions must be disclosed to participants during informed consent.

[Not all trials are appropriate for post-trial provisions including (but not limited to) early phase medicines with no safety/efficacy profile, 1 dose medicines, vaccines, or those where the sponsor does not have adequate data to make a benefit/risk assessment. Sponsors and researchers should assess each trial independently according to a set of established criteria. Post-trial provisions are dependent on the context and location of the trial, and may shift depending on the trial phase, illness, and local regulatory landscape and the local healthcare system. Ethics

Committees are responsible for assessing the risks and benefits of *the trial*, and are not equipped to assess the long-term, context dependent decisions of continued access to the medicine.]	
<u>Research Registration and Publication and Dissemination of Results</u>	
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 research study involving human **<u>participants</u>** ~~subjects~~ must be registered in a publicly accessible database before recruitment of the first **<u>participant</u>** ~~subject~~.
Comment:	
Paragraph 36	
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.	**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 **<u>participants</u>** ~~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

Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.	publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Comment:
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 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 **free of charge**. 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. **Trial participants should be notified when such reports are published.**

[The edits suggested here seek once again to improve transparency in clinical research and to remove financial barriers to accessing study reports.]

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 COVID-19. The 2013 language "may use" was previously inappropriately relied on to justify use of therapies proven **in**effective. The workgroup proposal now emphasizes that unproven intervention provisions (sometimes known as compassionate use) should not be used 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 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 or the legal and regulatory norms and standards for research.

Comment:

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 a~~An unproven intervention ~~is~~ may be 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 and benefits, and obtain informed consent. They must also keep detailed record~~s~~, ~~and~~ share data when appropriate or required by law, and avoid compromising clinical trials. Generally, the intervention should subsequently be made the object of research designed to evaluate safety and efficacy. These interventions must never be undertaken to circumvent the protections for research participants set forth in this Declaration or the legal and regulatory norms and standards for research.**

[Our major concern with the workgroup's proposed language is the implication that providing access in this fashion is an aspect of clinical research. While we acknowledge that data gathered in circumstances like those described in this paragraph are indeed valuable, we would like to stress the distinction between access of this sort and clinical research more explicitly.]

June 24, 2024

ADDITIONAL COMMENT TO THE WMA DoH WORKGROUP:
We would like to propose the following language be considered as a standard paragraph to guide a process for joint or reliance review.

When collaborative research is performed internationally, the research protocol must be approved by research ethics committees in every country where researchers intend to enroll participants and gather data. On occasions where the countries in question have formalized a system to permit one or more sites to rely on the decision of a single ethical review board, that single review board must perform a complete and detailed analysis of the local circumstances, context, laws, and regulations for each country intending to rely on its decision.

[We believe the increasing prevalence of multi-regional clinical trials demands the inclusion of a paragraph tailored to them within the Declaration. We believe this paragraph embodies the spirit of the Workgroup's proposed language to Paragraph 23, which we believe will provide greater clarity and effect as a standalone paragraph.]