



Sobre la revisión de la Declaración de Helsinki en 2024

RECOMENDACIONES REDBIOETICA UNESCO

Mayo 2024

A medida que el panorama de la investigación médica sigue evolucionando, impulsado por los avances tecnológicos y las crisis sanitarias globales, la Declaración de Helsinki (DH), emitida por la Asociación Médica Mundial (AMM), sigue siendo un marco ético importante para la investigación que involucra a seres humanos. La DH es un documento vivo que demuestra su compromiso con la adaptabilidad y su relevancia continua en la orientación de las prácticas de investigación ética en un escenario global en constante cambio. La DH es un documento que, aunque presente algunas limitaciones relacionadas con flexibilizaciones respecto de la protección de los participantes (versiones 2008 y 2013) en cuanto a temas como uso de placebo y acceso a beneficios post-estudio, sigue siendo un marco normativo menos problemático que otros parámetros internacionales, que son incluso menos protectores para los participantes.

Desde de la RedBioética UNESCO para América Latina y del Caribe, consideramos que la revisión de la Declaración de Helsinki de 2024 y en adelante debe abordar de manera integral los desafíos éticos emergentes y persistentes en el campo de la investigación médica, estimulados por emergencias sanitarias globales y rápidos avances tecnológicos. Las respuestas a la pandemia de Covid-19 muestran que es crucial equilibrar el progreso científico con la ética y la integridad, promoviendo el uso de diseños científicamente robustos, con estándares éticos universales, evitando el uso de intervenciones no comprobadas y garantizando el respeto por los derechos de los y las participantes y la distribución equitativa de los beneficios de la investigación. Además, los avances tecnológicos, incluyendo la inteligencia artificial y las tecnologías moleculares, exigen una vigilancia continua y un marco ético para asegurar que su implementación no solo sea segura y efectiva, sino también justa y accesible para todas las comunidades.

El proceso de revisión continua de la DH, iniciado por el Consejo de la AMM en abril de 2022 y liderado por la Asociación Médica Americana (AMA), implica una serie de encuentros regionales de especialistas en todo el mundo. Este enfoque colaborativo, supuestamente diseñado para fomentar el diálogo y moldear las enmiendas propuestas, enfatiza la importancia de la inclusión y del feedback de las partes interesadas a través de períodos de consulta pública. Sin embargo, el proceso de revisión de la Declaración se lleva a cabo exclusivamente en inglés, a pesar de que el español y el francés también son idiomas oficiales de la AMM. Esto ha resultado en la exclusión de una parte significativa de médicas, médicos y pensadores de países que no hablan inglés, y que representan más de 50% de los países, especialmente aquellos más pobres no tienen acceso a los recursos de traducción y sus voces no son debidamente escuchadas. Así, se privilegian los principios prevalentes en los países ricos en detrimento de otras realidades, perspectivas éticas y culturales de los países marginados, lo que puede exacerbar las vulnerabilidades, la explotación y la discriminación en los países pobres y de medianos recursos.

No es de ahora que la DH ha sido criticada por no atender adecuadamente las necesidades de entornos con escasos recursos, donde los estándares éticos pueden entrar en conflicto con las realidades locales. Además, en las últimas revisiones predomina una perspectiva utilitarista, donde la ética de las investigaciones se determina por los beneficios de sus posibles resultados, favoreciendo la adopción del doble estándar, permitiendo diferentes niveles de protección ética en países centrales y periféricos.

La última enmienda de la DH de 2013 eliminó la distinción entre investigaciones terapéuticas y no terapéuticas, un cambio apoyado por la Asociación Médica Americana desde 1997, se argumentó que la distinción entre estas dos categorías era defectuosa y no estaba de acuerdo con el pensamiento ético contemporáneo. Esta premisa es la actualmente adoptada en la Declaración de Helsinki. Por este motivo, la revisión de 2013 consolidó esta práctica, distanciando aún más las obligaciones de los médicos para con los pacientes en ensayos clínicos. Esto ha sido criticado porque se distancia de la Declaración de Helsinki de la Declaración de Ginebra, que se basa en los principios del Juramento Hipocrático y sostiene que la primera consideración del médico es con la salud y el bienestar del paciente y no con la investigación, la cual se realiza predominantemente en una lógica comercial que coloca los intereses financieros por encima del valor social de las investigaciones y del bien común de la humanidad. Además esta práctica debilita las obligaciones terapéuticas de los médicos investigadores y obvia el conflicto de interés de ser a la vez médico tratante y médico investigador de la misma persona.

Las versiones que siguieron a la revisión de 2000 flexibilizaron el uso de placebo en ensayos clínicos, permitiendo su uso incluso cuando había tratamientos comprobadamente eficaces, siempre que no causaran riesgos adicionales serios o irreversibles a los participantes. El principio de garantizar acceso a los mejores tratamientos comprobados después del estudio fue flexibilizado en las últimas revisiones de 2008 y 2013. En la última revisión, acuerdos previos entre países

anfitriones, patrocinadores e investigadores deberían determinar cómo se daría el acceso post-estudio, un cambio claramente insuficiente para proteger adecuadamente a los participantes.

Recomendaciones para la Revisión de la Declaración de Helsinki

1. Incluir los derechos humanos como parte esencial de la Declaración de Helsinki, alineándose con los principios bioéticos promulgados en la Declaración Universal sobre Bioética y Derechos Humanos (DUBDH) de la UNESCO.
2. Ser explícito en adoptar un estándar ético único y universal para todas las investigaciones, independientemente del país donde se realicen, con el fin de evitar el doble estándar - donde investigaciones consideradas inaceptables en países centrales son permitidas en países periféricos -, previniendo así la legitimización de la explotación y la discriminación.
3. Restablecer la distinción entre investigación terapéutica y no terapéutica. Esto facilitará, por ejemplo, las discusiones sobre el acceso post-estudio y el uso de placebos cuando existen intervenciones comprobadas.
4. Restringir el uso de placebos exclusivamente a situaciones donde se ha comprobado que no hay tratamientos comprobadamente eficaces, y así proteger a los participantes de la investigación de ser privados de terapias ya conocidas y efectivas.
5. Garantizar que los participantes de la investigación tengan acceso a las mejores intervenciones comprobadas después del término del estudio, según lo determinen sus médicos tratantes, por el tiempo que sea necesario o mientras la intervención se venda en condiciones monopólicas. Los patrocinadores deben ser responsables financieramente y los países deben decidir el proceso a seguir (por ejemplo, ensayo de continuación).
6. Conducir la revisión de los principios éticos de manera transparente e inclusiva, garantizando que todas las partes interesadas, especialmente los representantes de países en desarrollo tengan voz activa en el proceso. Esto es importante para asegurar que las revisiones sean justas y representen una variedad de perspectivas.
7. Garantizar que los participantes comprendan completamente la naturaleza de la investigación y sus diversas implicaciones mediante proceso dialógicos entre investigadores y posibles participantes. Esto incluye no solo la firma de un formato de consentimiento, sino también la garantía de un proceso mediante el cual se proporcione la información sobre la investigación de manera completa, comprensible y accesible para todos los participantes.
8. Restringir el uso de intervenciones no comprobadas y revisar aquellas normas de excepcionalidad adoptadas durante la pandemia, para evitar la flexibilización indebida de las evaluaciones éticas por parte de los Comités de Ética en Investigación (CEI).

9. Establecer mecanismos robustos de transparencia y responsabilidad para todas las etapas del proceso de investigación, desde la concepción hasta la publicación de los resultados. Esto incluye registros públicos de ensayos clínicos y divulgación completa de datos de investigación, especialmente cuando hay conflictos de interés.
10. Incluir un enfoque en derechos humanos en la capacitación y formación de los miembros de los CEI, asegurando que los principios de la Declaración Universal sobre Bioética y Derechos Humanos sean plenamente integrados en la evaluación ética de las investigaciones.

() Las opiniones aquí expresadas son responsabilidad de la Redbioética, las cuales no necesariamente reflejan las de la UNESCO y no deben comprometer a la organización de ningún modo. Las denominaciones empleadas y la forma en que aparecen los datos no implican de parte de UNESCO ni de la Redbioética, juicio alguno sobre la condición jurídica de países, territorios, ciudades, personas, organizaciones, zonas o de sus autoridades, ni sobre la delimitación de sus fronteras o límites.*

Declaration of Helsinki Public Comment Period Two

COMMENTING ORGANIZATION (if applicable):

- **Red Latinoamericana y del Caribe de Bioética da UNESCO – RedBioética**

COMMENT PREPARER (name and title):

- Fernando Hellmann, PhD (corresponding author)
- Susana María Vidal , MD, MsC
- Claude Verges de López, PhD
- Luis Alberto Sánchez-Alfaro, PhD
- Maria Virginia Rodriguez Funes, PhD
- Marianela Barcia, PhD
- Thiago da Cunha , PhD
- Xiomara Bu, PhD

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.

<p>Example 2013 DoH Language: The brown dog went fast.</p>	<p>Example Workgroup Proposal: The brown-dog went <u>really</u> fast.</p>
<p>Example Comment: The brown-dog went <u>really</u> fast <u>and completed the race</u>. [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.]</p>	
<p>Preamble</p>	
<p>Paragraph 1 <i>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.)</i></p>	
<p>2013 DoH Language: 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.</p> <p>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.</p>	<p>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 <u>participants</u>, including on identifiable human material and research and data.</p> <p>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.</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 2</p>	

*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:

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, research ethics committees and organizations involved in medical research, as they are fundamental to respect for and protection of all research participants, whether patients or healthy volunteers.

General Principles

Paragraph 3

No proposed changes.

<p>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.”</p>	<p>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.]</p>
<p>Comment: 3. The Declaration of Geneva of the WMA binds the physician with the words, “The health and well-being 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 The physician also has a responsibility to contribute to the health and well-being of the populations the physician serves and society as a whole, including future generations.”</p> <p>[This paragraph needs to be revised to align with the Revisions of the Declaration of Geneva in 2017 and the International Code of Medical Ethics in 2022.]</p>	
<p>Paragraph 4 <i>No proposed changes.</i></p>	
<p>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.</p>	<p>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.]</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 5 <i>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.</i></p>	

<p>2013 DoH Language: 5. Medical progress is based on research that ultimately must include studies involving human subjects.</p>	<p>Workgroup Proposal: 5. Medical progress is based on research that ultimately must include studies involving human subjects participants.</p> <p><u>Even the best proven interventions must should be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.</u> [Moved up from paragraph 6 (2013).]</p>
<p>Comment: 5. Medical progress is based on research that ultimately must include studies involving human subjects participants. <u>Even the best proven interventions must should be evaluated and continually refined through research for their safety, effectiveness, efficiency, accessibility, and quality.</u> [Moved up from paragraph 6 (2013).]</p>	
<p>Paragraph 6 <i>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).</i></p> <p><i>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.</i></p> <p><i>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.</i></p>	
<p>2013 DoH Language: 7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.</p>	<p>Workgroup Proposal: 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.</p> <p><u>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.</u></p>

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 **dignity of** all human subjects **participants** and protect their health and rights.

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

Meaningful engagement with potential and enrolled participants and their communities ~~should~~ **must occur before, during, and following the **medical research project**. Researchers should empower potential and enrolled participants and their communities to share their priorities and values; **patients and the public should** participate in study design, implementation, **as well as benefit from the research results** and other relevant activities; and engage in understanding and disseminating results.**

[To remind us of the Bill of Rights established in the United Nations’ Declaration on Human Rights and the International Declaration on Bioethics and Human Rights, “dignity” should be mentioned. See also CIOMS 2016 (guideline 7)]

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.

<p>2013 DoH Language:</p> <p>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.</p> <p>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.</p>	<p>Workgroup Proposal:</p> <p>6.7. The primary purposes 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.]</p> <p>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.</p>
<p>Comment:</p> <p>6.7. The primary purposes 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 provide social value 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.]</p> <p>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.</p> <p>[We do not agree with the proposed change. The term "social value" is key to capturing the broader impact of physician research, beyond individual and public health. While feedback indicates concerns about vagueness, removing the term altogether ignores the importance of considering the social benefits and ethical implications of research. Instead of eliminating "social value", we should clarify its definition to address the concerns raised]</p>	
<p>Paragraph 8</p> <p><i>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.</i></p>	
<p>2013 DoH Language: N/A</p>	<p>Workgroup Proposal:</p>

	<p><u>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.</u></p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 9 <i>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.”</i></p>	
<p>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.</p>	<p>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.</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 10 <i>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.</i></p> <p><i>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.</i></p>	
<p>2013 DoH Language:</p>	<p>Workgroup Proposal:</p>

<p>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.</p>	<p>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.</p>
<p>Comment: 10. Physicians, and other qualified researchers, and members of Research Ethics Committee 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.</p>	
<p>Paragraph 11 <i>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.</i></p> <p><i>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.</i></p> <p><i>The workgroup deleted “possible” and withdrew “and promotes sustainability,” and proposes adding “designed and” and “avoids or” to strengthen this paragraph.</i></p>	
<p>2013 DoH Language: 11. Medical research should be conducted in a manner that minimises possible harm to the environment.</p>	<p>Workgroup Proposal: 11. Medical research should be designed and conducted in a manner that avoids or minimises possible harm to the environment.</p>
<p>Comment: No comment on this paragraph.</p>	

Paragraph 12	
<p>2013 DoH Language: 12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.</p>	<p>Workgroup Proposal: 12. Medical research involving human participants subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.</p>
<p>Comment: No comment on this paragraph.</p>	
Paragraph 13 <i>No proposed change.</i>	
<p>2013 DoH Language: 13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.</p>	<p>Workgroup Proposal: 13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research. [No proposed change.]</p>
<p>Comment: 13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research. Their inclusion assumes that the research is aimed at producing information pertinent to their health needs. [For clarification of the meaning]</p>	
Paragraph 14	
<p>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</p>	<p>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</p>

<p>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.</p>	<p>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</p>
<p>Comment: 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 go on to become research participants subjects. Great caution must be taken to prevent conflicts of interest between researchers and providers. [For clarification of the meaning]</p>	
<p>Paragraph 15</p>	
<p>2013 DoH Language: 15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.</p>	<p>Workgroup Proposal: 15. Appropriate compensation and treatment for participants subjects who are harmed as a result of participating in research must be ensured.</p>
<p>Comment: 15. Appropriate compensation and treatment for participants subjects who are harmed as a result of participating in research must be ensured, and these requirements must be explicitly communicated during the informed consent process. [For clarification of the meaning]</p>	
<p>Risks, Burdens, and Benefits</p>	
<p>Paragraph 16</p>	
<p>2013 DoH Language: 16. In medical practice and in medical research, most interventions involve risks and burdens.</p>	<p>Workgroup Proposal: 16. In medical practice and in medical research, most interventions involve risks and burdens.</p>

<p>Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.</p>	<p>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.</p>
<p>Comment: No coments</p>	
<p>Paragraph 17</p>	
<p>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.</p> <p>Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.</p>	<p>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.</p> <p>Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.</p>
<p>Comment: No coments</p>	
<p>Paragraph 18 <i>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.”</i></p>	
<p>2013 DoH Language: 18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.</p>	<p>Workgroup Proposal: 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.</p>

<p>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.</p>	<p>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.</p>
<p>Comment: No comment on this paragraph.</p>	
<p><u>Vulnerable Groups and Individuals Individual, Group, and Community Vulnerability</u> <i>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.</i></p>	
<p>Paragraph 19 <i>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.</i></p> <p><i>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.</i></p>	
<p>2013 DoH Language: 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.</p>	<p>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. <u>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.</u></p>

Comment:
No comment on this paragraph.

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 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., with researchers and research ethics committees ensuring that specific protections are in place to safeguard their rights and well-being. [For clarification of the meaning]

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:

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.

Workgroup Proposal:

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:

Workgroup Proposal:

21. Medical research involving human subjects **participants must have social value and a scientifically sound and rigorous design and execution that are likely to produce reliable, valid, and valuable knowledge and avoid research waste and scientific misconduct. 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.

[Research without social value can be deemed "research waste." Thus, if "research waste" is to be mentioned in this paragraph, incorporating "social value" is essential. Moreover, it is important to include "scientific misconduct.]

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:

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

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

Workgroup Proposal:

22. The design and performance of each 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. [...] In clinical trials, the protocol must also describe **the guarantee of** appropriate **any post- trial provisions.** arrangements for post-trial provisions.

[For clarification of the meaning]

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:

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.

Workgroup Proposal:

23. The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning **and must have the independence and authority to resist undue influence from the researcher, the sponsor, or others.** and any other undue influence and must be duly qualified. **The committee must have sufficient resources to fulfill its duties, and its members and staff must collectively have adequate education, training, qualifications, and diversity to effectively evaluate each type of research it reviews.**

It 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**

	<p>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.</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Privacy and Confidentiality</p>	
<p>Paragraph 24 No comment on this paragraph.</p>	
<p>2013 DoH Language: 24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.</p>	<p>Workgroup Proposal: 24. Every precaution must be taken to protect the privacy of research participants subjects and the confidentiality of their personal information.</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 25 <i>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.</i></p>	
<p>2013 DoH Language: 25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be</p>	<p>Workgroup Proposal: 25. Informed consent is an essential component of respect for individual autonomy. Participation by individuals capable of giving</p>

<p>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.</p>	<p>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 agrees.</p>
<p>Comment: 25. Informed consent is an essential component of respect for human dignity and 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 agrees.</p> <p>[Addressing human dignity is even more fundamental than individual autonomy. In resource-limited settings, individuals often have no choice but to participate in research, meaning their autonomy is constrained. Additionally, in certain regions, "autonomy" is understood within the context of family and community relationships, emphasizing interdependence and interconnectedness. The concept of "dignity" can help avoid the narrow, individualistic view of autonomy typical of Western thinking.]</p>	
<p>Paragraph 26 <i>In public comment period one, the workgroup proposed added language to acknowledge increasingly common electronic methods of documenting informed consent.</i></p> <p><i>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.</i></p>	
<p>2013 DoH Language: 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.</p> <p>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.</p>	<p>Workgroup Proposal: 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.</p> <p>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</p>

<p>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.</p> <p>All medical research subjects should be given the option of being informed about the general outcome and results of the study</p>	<p>information and communication needs of individual potential subjects participants as well as to the methods used to deliver the information.</p> <p>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.</p> <p>All medical research subjects participants should be given the option of being informed about the general outcome and results of the study.</p>
<p>Comment:</p> <p>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, guarantee of post-trial study access and other provisions, such as transition from research to the health system care, and any other relevant aspects of the study. [...]</p>	
<p>Paragraph 27</p> <p><i>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.”</i></p>	
<p>2013 DoH Language:</p> <p>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.</p>	<p>Workgroup Proposal:</p> <p>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.</p>

Comment:

No comment on this paragraph.

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, **who must advocate for the will and best interests, 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.

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:

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.

Workgroup Proposal:

29. When a potential research subject **participant** who is deemed incapable of giving 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:

No comment on this paragraph.

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

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

<p>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.</p>	<p>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.</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 31 <i>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.”</i></p>	
<p>2013 DoH Language: 31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never adversely affect the patient-physician relationship.</p>	<p>Workgroup Proposal: 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.</p>
<p>Comment: No comment on this paragraph.</p>	
<p>Paragraph 32 <i>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.</i></p> <p><i>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</i></p>	

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:

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.

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:

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:

Physicians or other qualified researchers must **obtain ensure that** informed consent **is obtained** 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 and oversee the establishment and monitor ongoing use of such databases and biobanks. In exceptional situations where consent is impossible or impracticable to obtain, research on using stored data or biological material may be done proceed only after consideration and with the approval of a research ethics committee.

[enhances oversight]

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:

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Workgroup Proposal:

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where 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:

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s) existing, 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 non therapeutic 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; with risks being minimized through the implementation of effective mitigation strategies.

Extreme care must be taken to avoid abuse of this option.

[An example of non-therapeutic Medical research is in the aesthetic field, for example, without necessarily having a therapeutic or disease treatment objective]

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:

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Workgroup Proposal:

34. In advance of a clinical trial, sponsors, researchers and host country governments should make **post-trial** provisions for post-trial access **must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or 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:

Post-trial provisions

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, and researchers must ensure arrangements for post-trial access for all participants who still need an intervention identified as safe and effective in the trial, and provide a transition of care plan to the country's health system. These provisions must be accessible for as long as necessary or as long as the intervention is sold under monopolistic conditions, as determined by the participants' treating physicians. Sponsors should bear the financial responsibility for these provisions, and the host country should establish the process to be followed (e.g., continuation trial). Exceptions to these provisions must be approved by a research ethics committee. Specific information about post-trial provisions must be disclosed to participants during informed consent.

The benefits derived from any scientific research and its applications should be equitably shared with society at large and the international community, with a particular emphasis on Low-and-Middle-Income Countries. This includes not only access to the resulting knowledge and technologies but also the fair distribution of any economic gains, healthcare advancements, and improvements in quality of life.

["Pos Trial Provisions" do not only refer to "post-trial access" for the participant. It should also cover provisions for host communities and the social value of Medical research, especially regarding pandemics.]

Research Registration and Publication and Dissemination of Results

Paragraph 35

2013 DoH Language:

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

Workgroup Proposal:

35. Every research study involving human **participants** subjects must be registered in a publicly accessible database before recruitment of the first **participant** subject.

Comment:

35. Every research study involving human **participants** subjects must be registered in a publicly accessible database before recruitment of the first **participant** subject. **Information on the results of completing the study should also be recorded in this database.**

Paragraph 36

<p>2013 DoH Language: 36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.</p>	<p>Workgroup Proposal: 36. Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human participants subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.</p>
<p>Comment: 36. Researchers, authors, sponsors, editors, and publishers, and all stakeholders have ethical obligations with regard to the publication and dissemination of the results of research, following the principles of open science. 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. 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.</p>	
<p>Paragraph 37 <i>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 ineffective. 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.</i></p>	
<p>2013 DoH Language: 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</p>	<p>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</p>

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.

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 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 in jurisdictions where applicable regulations are absent, must first seek expert advice ethics committee review, weigh possible risks and benefits, and obtain informed consent. They must also record and share data when appropriate and avoid compromising clinical trials. A comprehensive scheme for monitoring the safety and efficacy of each case should be established through data accumulation. Additionally, a prospective or retrospective observational study should be conducted and reported to the Research Ethics Committee. 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, and must avoid compromising clinical trials.**