

## **World Medical Association Declaration of Helsinki 2024 Revision: Phase 1 Public Comment Document**

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### **Overview**

#### **Public Comment Period 1: Proposed Edits to Date**

Regional meetings held to date have so far focused on the following themes:

- Technological advancements, especially related to large-scale datasets, machine learning, artificial intelligence, and associated risks of privacy loss
- Use of placebo, no intervention, or less effective interventions in research trials
- Emerging and non-traditional trial designs
- Pandemics and other emergencies

A series of other issues arose at these regional discussions and workgroup meetings:

- Inclusive language that honors the rights, agency, and importance of participants in medical research.
- Recognition that human medical research participants include patients and healthy volunteers
- Consent for collection, storage, reidentification, and reuse of data, and alignment with the Declaration of Taipei
- Adequate resources, education, and experience for ethics review committees
- Importance of scientifically sound design to avoid research waste
- Importance of social value (including individual and public health) as additional purposes of conducting medical research
- Consideration of environmental impacts of medical research
- Interdisciplinary team-based research and whether the protection afforded by the Declaration's principles must extend to all medical research regardless of who is conducting it
- Recognition of electronic methods of documenting/recording freely given informed consent
- Responsibility to attempt to honor prior expressed preferences and values of research participants when consent must be sought from a legally authorized representative.

The resulting proposed edits (attached) affect the following sections of the Declaration:

- Paragraph 2
- Paragraphs 6 & 8
- Paragraph 11

- Paragraph 21
- Paragraph 26
- Paragraph 28 & 29
- Paragraph 32
- Paragraph 33

The workgroup seeks your comments, feedback, and suggestions related to these proposed edits. Please use the attached grid and return comments by 7 February 2024.

### **Public Comment Period 2: Remaining Potential Edits**

Following upcoming regional and special topical meetings related to different aspects of vulnerable populations<sup>1</sup>, the workgroup may propose additional edits which will be circulated in a second comment period this spring. These remaining meetings are likely to focus on:

- Research in lower-resourced (economically vulnerable) settings, specifically balancing the need to ensure access to the benefits of research participation while not targeting these communities for higher risk
- Specific vulnerable populations
- Engagement with communities and potential participants
- Reimbursement/compensation for participation in research
- Post-trial provisions and benefits
- Research inclusivity

Additional items that arose at prior regional meetings also remain under discussion by the workgroup, including:

- Clarifying the goals of paragraph 37 and the relationship between compassionate use of unproven interventions and research
- Consideration of the concept of justice
- Considering whether there is adequate language affirming the concept of patients as trusted partners in their own health and welfare

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<sup>1</sup> See <https://www.wma.net/> , under “Events,” for information on the remaining regional and special topical meetings.

**Public Comment Template**

<b>General Public Comments:</b>			
<b>DOH Paragraph</b>	<b>Current Text</b>	<b>Workgroup Proposed Amendments</b> Additions: <b><u>bold/underlined</u></b> Deletions: <del>lined out</del>	<b>Public Comments/Suggestions</b>
<p><b>Paragraph 2:</b> The regional session in Copenhagen reflected on the increasing interdisciplinary nature of medical research and the frequency with which physicians lead large teams. The workgroup strongly believes that <u>all</u> participants in medical research must share in the protections afforded by the Declaration of Helsinki regardless of who is conducting it, and thus that its principles should be upheld by all individuals and teams involved in such research. The proposed revisions below acknowledge that the Declaration is written by physicians but clarifies that its principles are fundamental to the protection of all human medical research participants.</p> <p>The new language also replaces “subjects” with “participants” out of respect for the rights, agency, and importance of those individuals. The workgroup proposes to consistently replace “subjects” with “participants” throughout the document. Finally, the new language recognizes that participants in medical research include both patients and healthy volunteers.</p>			
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.	<del>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.</del> <b><u>While the Declaration is written by physicians, the WMA holds these principles are fundamental to the protection of all human medical research participants, whether patients or healthy volunteers, and should be upheld by all individuals and teams involved in such research.</u></b>	<p>We believe this new language more effectively captures the breadth and scope of the Declaration of Helsinki.</p> <p>We respectfully suggest that WMA specifically mentions “including non-physician researchers and staff,” at the end of the sentence for emphasis. Specifically:</p>

			<p><u>While the Declaration is written by physicians, the WMA holds these principles are fundamental to the protection of all human medical research participants, whether patients or healthy volunteers, and should be upheld by all individuals and teams involved in such research, including non-physician researchers and staff.</u></p>
<p><b>Paragraphs 6 and 8:</b> Based on feedback heard at the Copenhagen session, workgroup members at their Kigali and Tokyo meetings expressed a desire to add specific mention of social value (including individual and public health) as additional primary purposes of conducting medical research in Paragraph 6. The workgroup’s proposed edits to paragraph 6 are below. This led to a need to update paragraph 8 to clarify and reinforce that the new reference to social value must not be misused as an excuse to perform medical research that fails to respect the rights of research participants.</p> <p>The workgroup also seeks feedback on two related issues:</p> <ol style="list-style-type: none"> <li>1) Whether paragraph 7 (without any current edits) should be moved to allow paragraph 6 to flow directly into paragraph 8, and if so, where paragraph 7 should be inserted.</li> <li>2) Whether the sentence in paragraph 6 beginning “Even the best proven interventions ...” should be moved elsewhere in the Declaration to improve the flow from current paragraph 6 to current paragraph 8, and if so, where.</li> </ol>			
6 and 8	6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve	6. The primary purposes of medical research involving human <del>subjects</del> <b>participants</b> <del>is</del> <b>are</b> to understand the causes, development and effects of	In Paragraph 6, we suggest numbering the causes for clarity as follows: “The primary purposes of medical research

	<p>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>7. <i>(For reference only)</i>. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.</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>diseases; <del>and</del> improve preventive, diagnostic and therapeutic interventions <del>(methods, procedures and treatments);</del> <b><u>and ultimately provide social value by advancing individual and public health.</u></b> Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.</p> <p>7. <i>(For reference only)</i>. Medical research is subject to ethical standards that promote and ensure respect for all human <del>subjects</del> <b><u>participants</u></b> and protect their health and rights.</p> <p>8. While the primary purpose of medical research is to generate new knowledge <b><u>that ultimately provides social value,</u></b> this goal can never take precedence over the rights and interests of individual research <b><u>participants</u></b> <del>subjects</del>.</p>	<p>involving human <b><u>participants are (i) to understand the causes, development and effects of diseases; (ii) to improve preventive, diagnostic and/or therapeutic interventions; and (iii) to optimize health and prevent or reduce illness for all people.</u></b> Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.”</p> <p>In Paragraph 8, we recommend augmenting the added text as follows: “While the primary purpose of medical research is to generate new knowledge <b><u>that ultimately advances individual and public health,</u></b> this goal can never take precedence over the rights and interests of individual research <b><u>participants.</u></b>”</p> <p>Note: Paragraph 7 can precede Paragraph 6, allowing Paragraph 6 to flow directly into Paragraph 8.</p>
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			<p>Note: We have grave concerns about the use of the term “social value,” without further definition. In the US, we have observed efforts to prevent scientific inquiry in certain areas (e.g., reproductive health, gender identity) justified by social value arguments. In our opinion, a broad, nonspecific term such as “social value” begs the question of who is deciding what is valuable to society. We believe it is better to be explicit about the goals of clinical research.</p>
<p><b>Paragraph 11:</b> The workgroup proposes the addition below to further emphasize the ethical importance of considering the environmental impacts of medical research when designing studies. The reference to environmental sustainability is consistent with language the World Medical Association adopted in revisions to the <i>International Code of Medical Ethics</i>.</p>			
11	<p>Medical research should be conducted in a manner that minimizes possible harm to the environment.</p>	<p>Medical research should be conducted in a manner that minimizes possible harm to the environment <b><u>and promotes sustainability.</u></b></p>	<p>We agree with this change, and we applaud WMA’s continued commitment to mitigating environmental impacts and promoting sustainability. Paragraph 11 would benefit from definition of the term “sustainability,” either in this paragraph or elsewhere.</p>

**Paragraph 21:** At several regional meetings, experts expressed concern about “research waste” where poorly designed medical research may consume resources and subject participants to risk without any chance of providing reliable, valid, or valuable information that might advance scientific knowledge or individual/public health. The workgroup proposes additional language in paragraph 21 to emphasize the ethical importance of ensuring scientifically sound design. The workgroup emphasizes that this addition would not prohibit well-designed research with low odds of a positive result (critical in clinical trials, for example, to test multiple candidate compounds for oncology therapies) or repeat trials to re-evaluate prior findings (as discussed in current paragraph 6).

21	<p>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.</p>	<p><b><u>Research involving human participants must have a scientifically sound design that is likely to produce reliable, valid, and valuable information.</u></b> <del>Medical research involving human subjects</del> <b>It</b> 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.</p>	<p>In Paragraph 21, we recommend the following addition to the first sentence: <b><u>Research involving human participants must have a scientifically and ethically sound design that is likely to produce reliable, valid, reproducible, generalizable, and valuable information.</u></b></p>
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**Paragraph 23:** In Sao Paulo and at other regional meetings, experts shared concerns that some research ethics review committees face challenges performing their duties, especially given the volume of research, increasing complexity of research protocols, and variability in resource support for these committees. The workgroup proposes new language to specify that these ethics committees must have sufficient resources to fulfill their important duties. Furthermore, the workgroup proposes language to specify that being “duly qualified” includes having adequate education and experience (which may include additional training resources).

<p>23</p>	<p>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.</p> <p>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</p>	<p>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. <b><u>It must have sufficient resources to fulfill its duties</u></b> and must be duly qualified <b><u>with adequate education and experience for its members and staff to effectively evaluate each type of research it reviews.</u></b> 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 <b><u>participants</u></b> <del>subjects</del> set forth in this Declaration.</p> <p>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</p>	<p>In the first part of Paragraph 23, we recommend the following changes:  <b><u>“The research ethics committee must have sufficient resources to fulfill its duties</u></b> and must be duly qualified <b><u>with adequate education and experience for its members and staff to evaluate each type of research it reviews effectively. The ethics committee should develop a process to consult with experts external to the committee with specialized education and experience whenever appropriate.</u></b> 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 <b><u>participants</u></b> set forth in this Declaration <b><u>nor any other fundamental human rights.</u></b>”</p>
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	<p>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>researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.</p>	
<p><b>Paragraph 26:</b> The workgroup agreed to update and clarify the language on documenting informed consent. The proposed addition acknowledges increasingly common electronic methods of documenting/recording freely given informed consent. A more minor change includes reordering words in the phrase “documented and witnessed” to “witnessed and documented,” as technically informed consent for an individual who cannot express themselves in writing must be first witnessed before then being documented.</p>			
<p>26</p>	<p>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.</p>	<p>In medical research involving human <del>subjects</del> <b>participants</b> capable of giving informed consent, each potential <del>subject</del> <b>participant</b> 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 <del>subject</del> <b>participant</b> must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without</p>	<p>We agree with the importance of freely given informed consent and the return of study results. Informed consent necessitates that the process occurs in plain language, in a language understood by non-medical personnel. The return of aggregate results to study participants and the larger community should occur as a matter of course. Because clinical trials may involve medical information and care important to the health of participants, participants should have access</p>

	<p>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>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>reprisal. Special attention should be given to the specific information needs of individual potential <del>subjects</del> <b>participants</b> as well as to the methods used to deliver the information.</p> <p>After ensuring that the potential <del>subject</del> <b>participant</b> has understood the information, the physician or another appropriately qualified individual must then seek the potential <del>subject's</del> <b>participant's</b> freely-given informed consent, <b><u>formally documented on paper or electronically.</u></b> <del>, preferably in writing.</del> If the consent cannot be expressed in writing, the non-written consent must be formally <del>documented and witnessed</del> <b>witnessed and documented.</b></p> <p>All medical research <del>subjects</del> <b>participants</b> should be given the option of being informed about the general outcome and results of the study.</p>	<p>to their individual results, when appropriate.</p> <p>We also note that “alternatives to participation” should be mentioned in the list of potential information relevant to an informed decision.</p> <p>Mention of accessibility of informed consent processes and forms should be included in the expectations for consent.</p> <p>Finally, there are some situations in clinical research in which documentation of informed consent is waived, or in which, for reasons of practicability in minimal risk research, the requirement for informed consent can be waived. Language has been suggested to accommodate these situations.</p> <p>For these reasons, we recommend the following changes in Paragraph 26:</p>
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			<p>“Unless specifically waived by the research ethics committee, all medical research involving human <b><u>participants</u></b> capable of giving informed consent, each potential <b><u>participant</u></b> 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, <b>alternatives to participation</b>, post-study provisions, and any other relevant aspects of the study <b><u>in plain language and in a language understood by the participant.</u></b></p> <p>The potential <b><u>participant</u></b> 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 <b><u>participants</u></b> as well as to the methods used to deliver the</p>
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			<p>information, <b><u>with particular focus on understandability and accessibility of participant-facing interactions and materials.</u></b></p> <p>After ensuring that the potential <b><u>participant</u></b> has understood the information, the physician or another appropriately qualified individual must then seek the potential <b><u>participant's</u></b> freely-given informed consent, <b><u>formally documented on paper or electronically-</u></b> If the consent cannot be expressed in writing, the non-written consent must be formally <b><u>witnessed and documented.</u></b></p> <p>All research <b><u>participants</u></b> and the larger community should be informed of the aggregate results of the study. <b><u>When appropriate,</u></b> individual results should be made available to research participants <b><u>and presented in plain, easily understandable language."</u></b></p>
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**Paragraphs 28 & 29:** Several speakers at the regional meeting in Tokyo expressed a desire to add language about the responsibility of researchers to attempt to honor any prior expressed preferences and values of a research participant when a researcher must seek consent from a legally authorized representative of the research participant. Below are proposed additions to paragraphs 28 and 29 to capture this. The workgroup also added “or other appropriately qualified individual” to acknowledge that consent is sometimes obtained by other members of a multidisciplinary research team. The workgroup is examining other paragraphs in the Declaration where a similar change may be warranted, but recognizes there are some places where the guidance specifically applies to physicians.

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.	For a potential research <del>subject</del> <b><u>participant</u></b> who is incapable of giving informed consent, the physician <b><u>or other appropriately qualified individual</u></b> must seek informed consent from the legally authorized representative, <b><u>taking into account any preferences and values previously expressed by the participant.</u></b> 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 <del>subject</del> <b><u>participant</u></b> , the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.	We agree with these additions to Paragraph 28.  Note however that there are reasonable exceptions to this statement, consistent with the ethical principles elucidated elsewhere in this document. For instance, specific mention of exception from informed consent requirements for emergency research (EFIC) should be made.
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	When a potential research <del>subject</del> <b><u>participant</u></b> who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician <b><u>or other</u></b>	We agree with these additions to Paragraph 29. We do, however, recommend specific mention of clinical research involving pediatric participants who cannot

	<p>addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.</p>	<p><b><u>appropriately qualified individual</u></b> must seek that assent in addition to the consent of the legally authorized representative, <b><u>taking into account any preferences and values expressed by the participant.</u></b> The potential subject's <b><u>participant's</u></b> dissent should be respected.</p>	<p>give informed consent by definition. We recommend concluding Paragraph 29 with the additional statement:</p> <p><b><u>"These expectations apply when the potential research participant is a child who is legally unable to give consent but nevertheless is able to articulate assent and other preferences."</u></b></p>
<p><b>Paragraph 32:</b> Following the regional meeting in Tel Aviv, the workgroup's consensus was 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 AI and machine learning, collection of genetic data, and risks of re-identification of deidentified data. The workgroup proposes a rewritten paragraph 32 (currently focused on material stored in biobanks) to also emphasize the importance of informed consent when identifiable (or re-identifiable data) are collected and stored as part of research, to include a cross-reference to the Declaration of Taipei (DoT) for details beyond these principles, and to highlight the DoT's most essential components related to human research.</p>			
32	<p>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</p>	<p><del>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</del></p>	<p>We have added language to illuminate the importance of accessibility and understandability of informed consent materials. We also suggest mention of express permission for genetic and/or genomic sequencing research.</p>

	<p>situations the research may be done only after consideration and approval of a research ethics committee.</p>	<p><del>the research may be done only after consideration and approval of a research ethics committee.</del> <b><u>Physicians and other researchers must obtain informed consent from research participants for the collection, storage, and foreseeable use of biological material and identifiable (or re-identifiable) data. Any storage of data or biological material for multiple and indefinite uses must 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, if possible. An independent 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.</u></b></p>	<p>We therefore propose to amend Paragraph 32 to:</p> <p><b><u>“Physicians and other researchers must obtain informed consent from research participants for the collection, storage, and foreseeable use of biological material and identifiable (or re-identifiable) data. Express approval for genetic and/or genomic sequencing research should be obtained. The informed consent process and materials should be accessible, in plain language, in the language of the research participant, and easily understood by non-medical personnel. Any storage of data or biological material for multiple and indefinite uses must 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, if possible. An independent ethics</u></b></p>
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			<p><u>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. This committee must be transparent in its functioning and must be independent of the researcher, the sponsor, and any other undue influence.”</u></p>
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**Paragraph 33:** The workgroup undertook an in-depth review of paragraph 33 on testing new interventions against placebos or against no intervention. This included a regional meeting in Sao Paulo with attendees from 10 Latin American countries and representatives from CONFEMEL and PAHO, and consideration of follow-up recommendations from CONFEMEL. Considering the importance of maintaining protection of research participants from inappropriate use of placebos, the workgroup is proposing the following edits to paragraph 33.

First, to clarify the exception that applies in the absence of proven interventions, the workgroup proposes the addition of the words “safe and effective.” For example, it may not be ethical to force participants to be exposed to a control arm of a trial in which the comparator intervention is the only proven effective one, but is known to be unsafe (where the risks or side-effects clearly exceed the benefits).

Second, to clarify that there can sometimes be more than one existing intervention with similar efficacy and safety (for example, two interventions that are tied for “best,” or times when there is uncertainty about which safe and effective intervention is best), the workgroup is proposing changing “best proven one” to “best proven one(s).”

Third, based on a suggestion from CONFEMEL, the workgroup proposes replacing “less effective” with “other” to clarify 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.

<p>33</p>	<p>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:</p> <p>Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or</p> <p>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.</p>	<p>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:</p> <p>Where no proven <b>safe and effective</b> intervention exists, the use of placebo, or no intervention, is acceptable; or</p> <p>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 <del>less effective</del> <b>other</b> 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.</p>	<p>We suggest including the terms “safe and effective” in the first sentence for consistency:</p> <p>“The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven <b>safe and effective</b> intervention(s), except in the following circumstances:”</p> <p>We also note that the determination of the “best proven intervention,” placebo or no intervention is particularly challenging in the context of pediatric research, given variation in a child’s age, maturity level, medical condition, and other situational factors.</p>
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	Extreme care must be taken to avoid abuse of this option.	Extreme care must be taken to avoid abuse of this option.	
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**Paragraph 34:** Although not included in the proposed revisions for the Phase I comment period, we at the MRCT Center find Paragraph 34 to be of critical importance to the future of the clinical research enterprise and therefore decided to offer proactive commentary on Paragraph 34 as it appears in the 2013 version of the Declaration.

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.	n/a	Ensuring access to treatments/interventions identified as beneficial during a clinical trial once the trial concludes is a crucial ethical obligation of clinical researchers. We recommend the following updates to Paragraph 34 be considered:  “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. <u>During the informed consent process, this information should be disclosed to participants verbally and in</u>
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			<p><u>written materials that are accessible, in plain language, in the language of the research participant, and easily understood by non-medical personnel. Specific attention should be given to how post-trial access will change if the beneficial treatment does or does not gain regulatory approval to be marketed in the region where the participant resides as well as information about how the participant will be notified whenever changes to post-trial access occur.”</u></p>
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