



HARVARD

Global Health Institute

June 15, 2013

Dr. Otmar Kloiber
Secretary General of the World Medical Association
By email to: doh@wma.net
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Dear Dr. Kloiber,

Please accept the following comments submitted on behalf of the *Multi-Regional Clinical Trials Center* at Harvard University (MRCT). We thank you for the opportunity to comment on the revised draft version of the Declaration of Helsinki, issued for public comment by the Counsel of the WMA in April 2013, following expert conferences Rotterdam, Cape Town, and Tokyo and appreciate the fine work done by the WMA working group in seeking to improve the Declaration's clarity and enhance human subject protection.

The MRCT Center at Harvard was formed in 2012 as a public-private partnership, focused on improving the planning and conduct of multi-regional clinical trials, especially those involving emerging markets. Our ongoing work includes programs to improve investigator and research team training, training of local investigators to serve as members of data and safety monitoring boards (DSMBs), tools for improving and simplifying Ethics Committee Review of protocols, and ways to share clinical trials data with third-party researchers. MRCT undertakes projects largely through the volunteer efforts of academic and industry experts. We also work with the government authorities of numerous countries, including the U.S. FDA, the European Medicines Agency, the PMDA of Japan, and similar agencies and ministries. Further information about the Center is posted at: <http://mrct.globalhealth.harvard.edu>.

Our comments on paragraphs 15, 22, and 34 of the April 2013 draft proposal follow.

Sincerely,

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<p>Working Group Proposal (April 2013 Annotated Draft)</p>	<p><u>MRCT’s Comments</u></p>	<p><u>MRCT’s Recommendations</u></p>
<p>Paragraph 15 (new paragraph)</p> <p>“Adequate compensation and treatment for subjects who are harmed as a result of participating in the research must be ensured.”</p>	<p>MRCT supports the notion that trial participants who are injured as a result of their participation in a clinical trial should have access to treatment and compensation; however, the reference to “harm” in the annotated draft is vague and the term “adequate” is especially vague.</p> <p>Despite the vague language, we don’t believe that the World Medical Association intends that mandatory compensation be established for harm that is the result of the natural progression of an underlying disease or condition. However, unless there is a clear standard to be used (for attributing responsibility for compensation), this language is likely to be very difficult to interpret and implement.</p> <p>The ambiguous wording in the proposal will complicate the process of securing third-party insurance for clinical trials in many regions, as well as the process of assessing the possible risks of a clinical trial, where the industry or academic sponsor and the research institutions choose to self-insure.</p> <p>In particular, Sponsors and research institutions seeking to ensure that adequate compensation is available will need to address the implications</p>	<p>MRCT supports language similar to that offered by Ezekiel Emanuel in the Lancet 2013; 381: 1532-33, noting that participants who suffer a “<i>direct</i>” injury from participating in research studies should be compensated.</p> <p>An alternative approach to be considered would be for Declaration to require that the protocol and informed consent materials clearly define the processes and standards for determining compensation, including assessing causation, the extent of harm, and the level or amount of such compensation.</p>

	<p>of such provisions, such as: (1) What kinds of possible harm are intended to be subject to compensation (e.g., physical, psychological, economic, social, or other injury); (2) how they would need to address compensation for short-term (typically resolvable) injuries and longer-term, impairment; (3) what injuries or kinds of injuries might reasonably be “related” to study participation, what the standard for determining that should be, and who is responsible for assessing relatedness (PI, EC, Sponsor) and what the process should be if the participants disagree, as seems likely in many cases; (4) whether and how to assess compensation for harm that potentially linked to the subject’s underlying medical condition, in whole or in part?</p>	
<p>Paragraph 22</p> <p>“The design and performance of each research study involving human subjects must be clearly described in a research protocol... The protocol should must describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.”</p>	<p>The proposed language stating that protocols must describe arrangements for <i>post-study access to interventions identified as beneficial in the study</i> suggests the every study would need to have such arrangements in place as a precondition for ethics committee or other approvals. It is important to acknowledge that post-trial access will not be available for a therapy unless there is a proven benefit and it is approved by regulators – both of these are unknowns at the protocol development stage. While this is appropriate for many studies, it should not be required for every study. For example, in the context of studies in healthy volunteers, there does not seem to be an ethical basis for making the drug available to study</p>	<p>We recommend that WMA make clear that this is not intended to be a universal requirement for all clinical trials; this can be done by adding language to clarify that it covers the “<i>relevant</i>” arrangements, i.e.:</p> <p><i>“The protocol must describe <u>the relevant and appropriate arrangements for post-study access by study subjects to interventions identified as beneficial in the study.</u>”</i></p>

	<p>subjects after the trial. Moreover, even in studies in patients, there are many considerations that make it difficult to describe such arrangements in advance; such as in trials comparing marketed drugs or interventions, where the sponsor may not own or have access to all of the study drugs or interventions, beyond purchasing the drug on the market.</p> <p>Another example of the difficulty of describing post-study access is in the case of an effectiveness trial involving an experimental drug that is shown to be of only limited efficacy (or a poor benefit-risk profile), and for which further development is thus abandoned. In such a case, even if a subject believes that he or she was helped by the study drug, it can be difficult to guarantee future availability of the study drug and thus difficult to describe such arrangements in advance.</p>	
<p>Paragraph 34 (new language)</p> <p>“...All study participants should be informed about the outcome of the study. ”</p>	<p>Study sponsors usually are blinded to patient identities and thus do not have any direct means of communicating those results. The principal investigator and his/her staff are typically the persons who have a direct relationship with the participants and who communicate directly with them. Presumably then, it is the Principal Investigator who would be expected to communicate such outcome information to participants, once such results are available. This of course would only work if the investigator were to continue to be in contact with the participants or if he or she were willing to locate them, after</p>	<p>We recommend changes to state that study participants should have “<i>reasonable access</i>” to information about the results of the study, in an appropriate consumer-friendly format, i.e.:</p> <p><i>“...All study participants should have <u>reasonable access</u> to information about the outcome of the study, preferably in a consumer-friendly format.”</i></p>

	<p>the trial is completed and the results become available.</p> <p>We also note that in some trials, study participants may choose to <u>not</u> be advised of the results of a study for various reasons. The Declaration should be respectful of the participant's right to choose to be informed or not.</p> <p>The outcome of the study is typically communicated in publications, regulatory filings, and on registries such as http://clinicaltrials.gov, but it is rare to disseminate outcome information from a single trial in a format intended for a layperson. Existing consumer-friendly information usually summarizes a body of information, rather than individual trials. The reason for this is because the results of a single trial are typically not dispositive. It thus is likely to be difficult to implement the draft proposal in paragraph 34, in the absence of reliable standards for communicating the full context around such information.</p>	
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