13 June 2013

To: World Medical Association
Re: World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects

The World Medical Association (WMA) has proposed updating the Helsinki Declaration, the international standard on human medical research, to offer more protection to trial participants. The WMA council will decide in October 2013 whether the revision should be forwarded to the general assembly for adoption. The following is the ISCTM response to the draft modifications to the Helsinki accord. The International Society for CNS Clinical Trials and Methodology (ISCTM) is a multi-disciplinary independent organization, devoted to promoting advances that address strategic, clinical, regulatory, methodological and policy challenges that arise in the development and use of CNS therapeutic agents. The ISCTM is a partnership of persons in academia, industry, government, policy-making, and the public. The following remarks reflect our expertise and experience in CNS research and may be applicable to other areas of research.

The ISCTM formed a Working Group, chaired by Steven Potkin, MD, to review and provide comments. Authors (in alphabetical order):

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WMA Declaration of Helsinki Working Group
Draft revised text for public consultation, 15 April – 15 June 2013

COMMENTS ON SPECIFIC LINES IN THE REVISED DECLARATION:

	Preamble	Response comments
15	Adequate compensation and treatment for subjects who are harmed as a result of participating in the research must be ensured.	It is the obligation of the researcher to ensure that subjects who are harmed receive adequate treatment including associated medical costs for their injuries. Subjects exercising their autonomy voluntarily enter protocols in which the knowable risks have been described as well as the potential for unforeseen risk. Given this disclosure and their voluntary agreement to participate financial compensation beyond treatment is typically not appropriate. Alternative text: Appropriate ~~adequate compensation and~~ treatment for subjects who are harmed as a result of participating in the research must be ensured.
20	Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and the research cannot be carried out in a non-vulnerable population. In addition, ~~and if there is a reasonable likelihood that~~ this population or community should stand~~s~~ to benefit from the knowledge, practices or interventions that result from the ~~results of the~~ research. Consideration should also be given to ensuring that the community receives a fair level of additional benefits.	A disadvantaged or vulnerable population should benefit from the knowledge, practice or interventions that result from the research that affects the disadvantaged or vulnerable population either generally or disproportionally to majority population. The suggestion for ensuring that the community receives a fair level of additional benefits beyond that previously stated is too vague to be practical and may inadvertently preclude early or exploratory foundational research the implications of which are difficult if not impossible to predict. In addition, the concepts of disadvantaged and vulnerable population are not overlapping. It is ethically problematic to refuse a disadvantaged/minority population member the right to participate in research until research has been completed on the advantaged/majority population. As participation in research can result in potential benefits, in addition to potential risks, creating barriers to participation can further perpetuate discriminatory practices singling out the disadvantaged population (see Denny and Grady, J Med Ethics 2007;33:382–

		385. doi: 10.1136/jme.2006.017681 for rationale) Alternative text: Omit entire sentence beginning with "Consideration…" Delete "disadvantaged"
22	The protocol must describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study.	The protocol should describe any access to post-study interventions that have been identified as beneficial in the study. In early studies, there may be apparent benefit, however, later studies may alter the understanding of that benefit in terms of efficacy and safety and therefore not support continued use of the intervention. Research is carried out to ensure that premature decisions on efficacy and safety are not made thus unnecessarily exposing subjects to interventions without adequate supporting data benefit. Demonstrating safety is a complicated process typically involving more than a single study and needing regulatory approval. Therefore, there is no necessary obligation that apparently beneficial interventions be made available to subjects as this depends upon intervention availability, safety data, logistic realities and regulatory status. (*e.g*. a Phase 2 safety study might not support continued or extended treatment, and may not be supported by later acquired Phase 3 data). Alternative text: The protocol must describe arrangements for post-study access by study subjects to interventions identified as safe and beneficial in the study, if available to sponsor and investigator, and have required local regulatory approval.
23	At the end of the study, the investigators must submit a final report to the committee containing a summary of the study's findings and conclusions.	This information is available at ClinicalTrials.gov or other trial registries for most research. The individual researcher and the site may not have control over the analysis or timely access to all the data from a multi-site study precluding the submission of such data to the IRB committee at the end of the study. The subject-level data may remain

		blinded until after submission to regulatory authorities. Alternative language: At the end of the study, if not available on ClinicalTrials.gov, or another trial registry, the investigators should submit a final report to the committee containing a summary of the study's findings and conclusions when it becomes available.
33	The use of placebo~~,~~ or no ~~treatment~~intervention~~,~~ is acceptable in studies where no ~~current~~ proven intervention exists; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, placebo or no treatment 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 treatment will not be subject to ~~any~~ 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.	The concept of a proven or best proven intervention is difficult to clearly define, and has various definitions by different stakeholders, and at different stages of the research process, and may not be appropriate for all populations because of various co-morbidities, subpopulations, effects of specific medications and dose. Additionally, individuals in all settings may not have access to proven intervention. Numerous studies have demonstrated that there are positive effects of receiving placebo in a research study. The goal of many studies is to determine what benefit, if any, an experimental treatment has over the benefits of placebo. That said, there must be compelling, scientifically sound reasons for the use of placebo or no treatment. Avoiding foreseeable serious or irreversible harm from an investigational intervention or from not treating underlying disease is an appropriate concern for all studies. However, this can never be guaranteed. Serious or irreversible harm must be distinguished from temporary pain or discomfort that can accompany research participation. Based on the demonstrated value of placebo in establishing efficacy and safety, "extreme" care may be too proscriptive. Alternative language: … will not be subject to ~~additional~~ foreseeable risk~~s~~ of ~~serious or~~ irreversible harm as a result of not receiving the best proven intervention. ~~Extreme~~ Careful consideration must be taken to avoid abuse of this option.

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 study. This information should also be disclosed to participants during the informed consent process. All study participants should be informed about the outcome of the study. ~~At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.~~	Consent should include discussion of any provisions for post-trial access to a treatment identified as beneficial if available. Access to such treatments may be limited by current safety data, intervention availability, and regulatory considerations. Provision for documenting subject's wish to be informed of study outcome should be provided along with explanations of the envisioned timeline for such disclosure after the entire study is completed. Alternative language: In ~~advance of~~ planning a clinical trial, sponsors, researchers and host country governments should when possible make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the study. This information should also be disclosed to participants during the informed consent process. All study participants should have the opportunity to be informed about the outcome of the study.

The International Society for CNS Clinical Trials and Methodology (ISCTM) offers these comments and suggested language for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group received compensation for comments provided. Comments represent personal opinions and not that of the institution, agency, or company affiliation of Working Group members. The ISCTM welcomes dialogue with the World Medical Association and other groups concerned with conducting research in a humane and ethical manner in order to improve the outcome for those suffering from CNS disorders.