American Medical Association
Physicians dedicated to the health of America

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The Honorable Tommy Thompson
Secretary
U.S. Department of Health and Human Services
Dockets Management Branch HFA-305
Docket # 02N-0475
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket # 02N-0475
Draft Guidance Document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection"

Dear Secretary Thompson:

The American Medical Association (AMA) is deeply committed to the study, application, and advancement of scientific knowledge to provide competent medical care for patients, as clearly stated in our *Principles of Medical Ethics*. Drawing from several other AMA policies that relate to ethical conduct in research, we respectfully submit these comments regarding financial relationships and conflicts of interest in human subject research.

Identification and Disclosure of Financial Conflicts

Identification of Financial Conflicts

The federal guidelines suggest that Institutional Review Boards (IRBs), investigators, and institutions consider questions, such as how to identify interest created by financial relationships, including whether individuals receive "significant payments of other sorts."

The AMA recognizes that physicians have fundamental obligations to develop and maintain patient trust by providing competent and compassionate care. To ensure that there are no adverse effects from financial relationships established in the context of research, it is important first to identify potential conflicts of interest to be able to manage them. Such adverse effects include negatively impacting patients and undermining the integrity of the research. Indeed, when actual or perceived financial conflicts of interest are identified and managed, it is possible to prevent the erosion of this fundamental trust.

Through the work of its Council on Ethical and Judicial Affairs (CEJA), the AMA has adopted two specific positions regarding financial conflicts of interests in research. AMA Opinion E-8.031, "Conflicts of Interest: Biomedical Research," of the AMA *Code of*

Medical Ethics addresses the importance that the medical community "[avoid] real or perceived conflicts of interest in clinical research ...to ensure objectivity and maintain individual and institutional integrity." Additionally, AMA Opinion E-8.0315, "Managing Conflicts of Interest in the Conduct of Clinical Trials," details the ethical considerations that physicians must assess to manage and reduce financial conflicts of interest.

Notably, AMA policy does not distinguish between "significant" and "insignificant" financial conflicts of interest. The AMA has determined that appropriate management strategies should be determined by assessing the risk of harm to the research participants and the risk of undermining the integrity of the research.

Disclosure of Financial Interests
The federal guidelines also request that IRBs, investigators, and institutions consider whether disclosure of the financial interest to prospective subjects is warranted.

The AMA acknowledges two important options that may assist in the management of financial conflict of interests. Full disclosure of the physician-investigator's financial interests should be made to institutions involved in research oversight and should be included as part of the informed consent process. Another strategy may include voluntary recusal from research projects where disclosure of financial interests may be an insufficient safeguard to protect participants. In sum, the AMA encourages proactive mitigation or elimination of all conflicts of interest in clinical research.

Institutional Level

The federal guidelines recommend that institutions engaged in federally conducted or supported research establish conflict of interest committees or identify other bodies or persons to deal with financial interests in research.

In AMA Policy H-460.921, Support for Institutional Review Boards, the AMA acknowledges the importance and value of IRB review and safeguards. Concurrently, the AMA encourages increased support, funding, and resources by various sources to allow IRBs to appropriately meet ethical and regulatory guidelines for the protection of human research participants.

The federal guidelines have identified and described a mechanism entitled "conflict of interest committees" (COICs) as an additional safeguard to protect human research. Without question, the need for clear documentation, deliberation, and review of conflicts of interest is appropriate. However, the AMA believes that no singular mechanism will be unequivocally accepted by the vast range of medical centers and institutions. Instead, we recommend that IRBs be permitted to conduct the functions of the COICs. Otherwise fiscal and staffing implications inherent in requiring separate, independent COICs may prove too burdensome for some institutions.

It is also important to consider that an increasing proportion of research is conducted by community-based physicians outside of academic medical centers and, therefore, may not be within the purview of institutional COICs, although such research would always be governed by a protocol that is reviewed by an IRB. Under such circumstances, blending the COICs' functions with those of IRBs may prove to be a more comprehensive approach.

Financial Interests of Physician-Investigators

Physician-Investigators and Comprehensive Informed Consent

Finally, the federal guidelines recommend that investigators consider the "potential effect that any financial relationship may have on a clinical trial, including interactions with research subjects, and to consider using special measures to modify the consent process when a potential or actual financial conflict exists."

The AMA recognizes that physicians may have financial interests in research that conflicts with the best interests of the patient. In AMA Opinion E-8.03, "Conflicts of Interest: Guidelines," it is strongly stated that "under no circumstances should physicians place their own financial interests above the welfare of their patients." Moreover, according to AMA Opinion E-8.0315, physicians should divest themselves of significant conflicts of interest before engaging in clinical research or should voluntarily recuse themselves in instances where patient safety or research integrity may be compromised.

In general, the AMA considers the informed consent process to be instrumental to the protection of research participants. A comprehensive informed consent process by the physician includes oral disclosure of financial and other conflicts of interest to the patient or surrogate decision-makers, as well as being included in the written informed consent. The disclosure on the document should be clear, succinct, and provide all material information to the patient and/or surrogate decision-maker about the financial conflict of interest. In addition, the AMA supports a special mechanism whereby physicians voluntarily self-identify themselves as physician-investigators to other health care professionals and staff involved with the care and management of the patient. This additional mechanism would reduce potential undue influence that may arise from conflicts of interest, and also to ensure that the distinction between clinical care and research remains transparent.

Amount of Disclosure Regarding Financial Conflicts

Finally, the federal guidelines recommend that investigators consider "including information in the consent document such as source of funding."

In accordance with AMA Opinion E-8.0315, physician-investigators should always disclose information pertaining to the source of funding to patients both orally and in the written consent document. Physician-investigators should also identify and disclose future proprietary or interests, such as licensing or patent applications both orally and in the

written consent document. It is worth noting that AMA Opinion E-2.08, "Commercial Use of Human Tissue," encourages physicians who are contemplating the commercial use of products derived from research to disclose to patients those potential commercial applications before a profit is realized.

Altogether, these AMA policies provide a framework that favors full and comprehensive disclosure in obtaining patient informed consent from a research participant, including the physician's and the participant's acknowledgement that potential financial conflicts were adequately disclosed. The AMA also strongly encourages physician-investigators to tailor their explanations and disclosures so as to ensure adequate understanding by the patient.

Conclusion

The AMA commends HHS in its efforts to minimize actual conflicts, as well as the appearance of impropriety, in the conduct of human subject research. As a final note, we wish to make clear that physician-investigators should follow all federal and regulatory guidelines, in addition to following professional association guidelines governing the ethical obligations for disclosure to patients regarding any financial interests held by a physician-investigator. We are grateful for the invitation to submit comments, and if we can be of further assistance, please contact us.

Sincerely,

Michael D. Maves, MD, MBA