CASE WESTERN RESERVE UNIVERSITY

May 30, 2003

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

RE: Docket No.02N-0475, Draft "Financial Relationships and Interest in Research Involving Human Subjects: Guidance for Human Subject Protection"

Dear Secretary Thompson:

As a leading academic and research institution Case Western Reserve University (CWRU) is committed to protecting the safety of our research participants and the integrity of our research. We share the Department of Health and Human Services' goal of upholding the highest ethical standards for all research activities. We recognize that careful management of potential conflicts of interest is vital to maintaining public trust and confidence, protecting research subjects, and preserving objectivity of research. CWRU applauds the Department for its efforts to increase awareness and to improve public confidence in those who carry out human subjects' research, including the draft "Financial Relationships and Interest in Research Involving Human Subject Guidance for Human Subject Protection."

The University is pleased that this current draft focuses explicitly on ways financial interests might affect the rights and welfare of human subjects. It directs the Institutional Review Board's attention to determining the best process for protecting human subjects, leaving the review of financial relationships and management of financial interests to the institution. Case Western Reserve works to ensure the fundamental integrity of its research through implementation of policies and programs to guide our faculty, students, and staff in maintaining the very highest research standards, including financial relationships. Our activities reflect many of the approaches described in the Department's guidance.

Use of Alternative Approaches

Case Western Reserve appreciates the Department's clarification that its intent is to provide guidance for human subjects protection without changing existing regulations or imposing new requirements. This is reflected in the first footnote, that "an alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations." The

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University believes that this endorsement of alternatives is significant enough that it should be included in the main body of the text rather than being consigned to a footnote. The guidance will be more effective if it includes a clearer, more prominent reminder to the research and regulatory communities that the guidance encourages universities to seek the very best strategies to protect human subjects – including alternative strategies tailored to the unique characteristics and culture of each institution. This allows us to retain flexibility in managing potential conflicts by permitting us to adopt the management tools that are most effective within our particular governance structure and to adapt conflict management to the specific circumstances presented.

The real strength of the revised Guidance is the manner in which it asks thought-provoking general questions and points for consideration – a device used in the first two parts of Section II, A, General Approaches, and B, Points for Consideration. This approach should be carried through the third and final part II.C, Specific Issues for Consideration. This type of rhetorical device challenges the university, IRBs and investigators to describe current practices and consider different solutions or mechanisms rather than prescribing specific actions. We are acutely concerned that the specific recommendations characteristic of many of the bulleted items in section II.C will become a checklist used by federal regulatory and audit agencies and office to determine compliance and fail to achieve the Department's goal of guidance to ensure the protection of human subjects.

Guidance for Institutions, IRBs and Investigators

Some of the Specific Actions for Consideration in section II.C raise particular concerns and we offer the following recommendations.

Section II. C. 1. Institutions

We support the recommended guidelines set out with respect to potential institutional conflicts of interest, and make the following suggestions for improvement.

a. With respect to the guideline "**[u]se independent organizations to hold or administer the institution's financial interest**," we believe the use of such an independent organization may not be necessary or appropriate in many circumstances. The focus for managing institutional funds to prevent potential institutional conflicts of interest should be on separating the research function from the administration of funds related to the research. Institutional investments may be managed by adequately separated administrative units that, while technically within the broad legal boundaries of the institution's organization, are sufficiently independent from the management of the research function to adequately mitigate a potential or perceived institutional conflict of interest. This may be especially true with respect to financial interest held in pooled institutional holdings, mutual funds, and other aggregated holdings. The protection of

institutional assets is so fundamental to an institution that divesting management of this responsibility is neither desirable nor practical in many circumstances.

We suggest this guideline be re-worded to read "**[[e]stablish the independence of intuitional responsibility for research activities from the management of the institution's financial interests.**"

b. With respect to the language "**[e]stablish policies regarding the types of relationships that may be held by parties involved in the research and circumstances under which those financial relationships and interests may be held**" we suggest revising that language to read "**[e]stablish policies or guidelines regarding the types of relationships that may be held by parties involved .... may be held.**"

This additional language is consistent with the Department's flexible, case-by-case framework integrated into the Draft Guidelines, as set forth above in comment 1, and will clarify a potential ambiguity in the draft language. As written, this guideline may be construed to establish a guideline advocating policies with specific, quantified rules regarding "the types of relationships that may be held" and "circumstances under which those financial relationships and interests may be held." Given the complexity and diversity of conflict issues, the most effective management of conflicts is not to create policies with blanket "one-size-fits-all" rules to address conflicts. Instead, institutions may seek to establish "guidelines" that may be tailored to each situation. Such guidelines may provide the most effective conflicts management.

Section II. C. 2. IRB Operations

We support the recommendations in this section. They reflect the regulatory requirements at (45 CFR § 46.107(e), 21 CFR § 56.107(e)). Many IRBs have already implemented these requirements.

Section II. C. 3. IRB Review

We support the intent of the language in this section, but not the vesting of responsibility in the IRB. We believe that this essential function can be managed by other institutional entities such as a "Conflict Management Review Committee" which has as its sole charge, to review cases where a perceived conflict of interest may affect the research project or the protection of subjects. With appropriate and routine contact with the IRB, a committee of this nature can communicate concerns to the IRB which require IRB action or recommend disclosure to study subjects. The IRB can then act on the recommendations of that committee. We suggest revising the language to identify this obligation as "Institutional" and charge each **institution** ... "....**reviewing HHS conducted or supported human subjects research or FDA regulated human subjects research consider the following actions ....**" . Formalized non-IRB mechanisms for review and implementation of these standards should be considered acceptable. Vesting more review

responsibilities within the role of the IRB may dilute their current role and divert their attention from protection of subjects with respect to risks and harms of the research project and focus their attention on other institutional management issues such as conflict of interest.

Section II. C. 4 Investigators

a. The draft guidelines suggest "**[c]onsidering independent monitoring of the research, e.g. using a data and safety monitoring committee.**" We fully support endorsing the important role independent monitoring plays in the context of conflicts in human subjects research. We believe that independent monitoring may effectively take place under the auspices of a research compliance function that is adequately separated from the conduct of research. While a "DSMB committee" is one method to achieve monitoring of certain aspects of clinical trials , we recommend the draft language also give as an additional example "establishing an independent monitoring program." For example, at the University of Minnesota we have established a post-approval monitoring program that audits compliance with all aspects of the regulations governing the use of human subjects in research. This includes conflict of interest, adherence to IRB stipulations, informed consent, adverse event reporting, HIPPA compliance, drug labeling, Biosafety compliance, etc.

Additional Guideline Recommendations

a. ***Prefatory Language***
The Department should consider whether additional language should be included in the prefatory language to the guidelines regarding current efforts by many in the research community to prevent and manage potential financial conflicts of interest. Often, highly publicized but isolated events unduly erode public trust in highly valuable research. The Department should acknowledge that many research institutions—and we believe we are among them—already actively and successfully manage potential financial conflicts of interest in human subject research and utilize many of the recommended guidelines. The public, through comments from the Department and elsewhere, should be assured that the research community proactively has taken many steps to assure financial interests do not compromise subjects' safety or jeopardize the integrity of research. The Department should balance these guidelines with such language to limit any misperception these guidelines may cause to suggest that conflicts of interest have made research at institutions unsafe or impugned the quality of human subjects research generally.

b. ***Continuing Dialogue***
The Department should insure that it works closely with the research community as it monitors the affect of these proposed guidelines and the proactive activities taken by research institutions, IRBs and investigators. The research community has been, and will

continue to be, proactive in managing financial conflicts of interests. As a member of that community, we respectfully request active dialogue and continuing discussion. This communication will be especially critical if the Department moves to formalize the guidelines into a proscriptive regulatory framework.

Thank you for the opportunity to provide comments on the draft guidance.

Sincerely,

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Provost and University Vice President

cc: Edward M. Hundert
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