UNIVERSITY OF MINNESOTA

May 23, 2003

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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 Subject: Guidance for Human Subject Protection"

As a leading academic and research institution committed to protecting the safety of our research participants and the integrity of our research, the University of Minnesota appreciates the Department's initiative to provide additional guidance on the management of potential conflicts of interest in human subjects research. We recognize that careful management of potential conflicts of interest is central to maintaining public trust and confidence, protecting research subjects, and preserving the objectivity of research. Accordingly, we support the Department for taking this, and other initiatives to increase awareness and to improve public confidence in those who carry out human subjects research. As a partner in this effort, we offer the following comments and suggestions in response to Department's Draft Guidelines.

1. Proposed Program Framework.

The University of Minnesota commends the Department for recognizing the complexity of conflicts management by establishing "guidelines" rather than blunt, proscriptive rules. By preserving this framework, the Department appropriately acknowledges that the relationships among government, academia, industry, and others often involves legitimate financial relationships which neither cause conflicts of interest nor harm to human subjects. Rather, each potential financial conflict situation raises unique concerns. The most effective way to manage many conflict of interest situations is accordingly on a case-by-case basis. Often, the financial interests of researchers or an institution do not create a conflict, or, where the potential for a conflict exists, proactive management is sufficient to avoid an actual conflict that could affect research or research subjects.

Assuring that research institutions retain flexibility in managing potential conflicts allows us to adopt the management tools that will be most effective under our particular governance structure and to tailor conflict management to the specific circumstances presented. Conflicts tools will, as recognized by the Department's draft guidelines, be most effective when developed by the particular institution that will use them for these reasons. Requiring a specific management practice, "hard and fast" rules for identifying and managing actual conflicts, or enumerating specific situations to be

02N-0475 C17

flatly prohibited, however, may create ineffective, impractical, or unnecessary conflict management systems which unduly limit research and do not adequately protect research subjects.

The Draft Guidelines provide, along with recent contributions provided by the research community itself, significant guidance for research institutions to consider when evaluating their conflicts management programs. The University of Minnesota strongly urges the Department to maintain this programmatic approach and flexibility in the final Guidelines, as well as in future and related activities in this area.

2. Specific Issues for Consideration.

"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 to improve them:

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 interests 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 <u>or guidelines</u> 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."

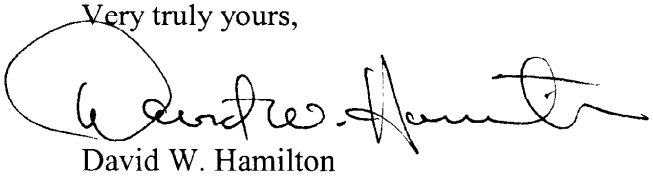
a. The draft guidelines suggest "**[c]onsidering independent monitoring of the research, e.g. using a data and safety monitoring committee.**" We fully support endorsing the important role independent monitoring plays in the context of conflicts in human subjects research. We believe that independent 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.

3. Additional Guideline Recommendations.

a. Prefatory Language. We request the Department 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 that 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 Dialog. The Department should ensure 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 dialog and continuing discussion. This communication will be especially critical if the Department moves to formalize the guidelines into a proscriptive regulatory framework.

Very truly yours,



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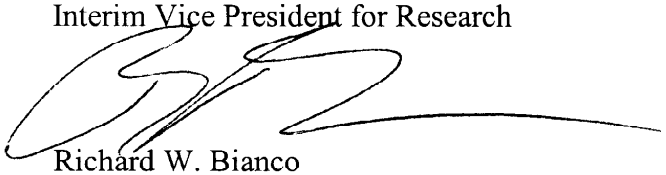

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