

Re: Draft Interim Guidance on Financial Relationships in Clinical Research, Issued by the National Human Research Protection Advisory Committee

Dear Ms. Gottfried:

This letter is in response to the request for comments on the Draft Interim Guidance referenced above and issued on January 10, 2001. I request that you accept my late comments and include them in your analysis.

The Department of Health and Human Services (DHHS) is justifiably concerned about the actual or potential effect of conflict of interest in the conduct of human research. Though I applaud the initiative of the DHHS in promulgating a guidance document for addressing conflict of interest (COI) issues, it does not go far enough. The document, unfortunately, does little to recognize the distinct charges and expertise of a COI committee and an Institutional Review Board (IRB). It, therefore, adds little value to the currently available guidance or ensuring the review of research upholds the ethical principles outlined in The Belmont Report, specifically, the importance of human subject autonomy and dignity as expressed through the process of informed consent.

Dignity and Autonomy

To ensure the rights of a subject is to acknowledge their dignity and autonomy. The concept of dignity describes a state of being worthy or having intrinsic worth. To subject a person to an indignity is to say they have no worth, that they are not worthy of our respect. The ethical principles, guidelines, and regulations for human research require us to treat research subjects with dignity. The ethics of informed consent are based in the concept of dignity. We express our respect for individual dignity by acknowledging the autonomy of each human subject through the process of informed consent. The National Commission for the Protection

of Human Subjects in Biomedical and Behavioral Research highlighted in The Belmont Report:

"To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so."

Furthermore, the California Supreme Court in their decision *Moore v. The Regents of the University of California*, highlighted, "[A] physician who treats a patient in whom he also has a research interest has potentially conflicting loyalties. This is because medical treatment decisions are made on the basis of proportionality - weighing the benefits to the patient against the risks to the patient.... The possibility that an interest extraneous to the patient's health has affected the physician's judgment is something that a reasonable patient would want to know in deciding whether to consent to a proposed course of treatment." Additionally, the California Association of Hospitals and Health Systems noted, "Prior to consenting to treatment, patients have the right to be informed of any potentially conflicting interests (viz., medical research or economic interests) that a physician may have related to such treatment." The guidance document suggests that institutional administrative bodies, such as a COI committee, review disclosures of financial relationships and then share only "problematic" findings with the IRB. We should examine the differences between a COI committee and an IRB to determine their respective expertise, responsibilities, and the methodology to ensure the protection of the rights and the welfare of the human subjects.

Institutional Review

A research institution should have two entities examining, for different purposes, an investigator's financial relationship with a study sponsor in order to address a possible conflict of interest (COI): the IRB and the COI committee or institutional official responsible for COI review. Though the two entities are mandated to examine an investigator's possible COI, they

do so under distinct and separate charges.

Responsibilities of the COI Committee

We should remember that a COI committee is responsible for the review of positive financial disclosures in proposed research projects in order to manage or avoid, real or perceived potential conflicts of interest of the investigator and/or the institution. The COI committee, or an institutional official, determines if there is a financial COI that warrants steps to ensure the integrity of the research, the investigator, or the institution.

These steps may include requesting the implementation of a mechanism to avoid an appearance of a COI by changing the nature of the involvement of the investigator in the research, name a different principal investigator, changing the terms of the agreement with the sponsor, etc. The charge of the COI committee does not include the protection of the rights and welfare of human research subjects nor does it include training in the concepts of informed consent, nor does such a committee include non-affiliated or non-scientific members to help address community standards for such disclosure.

Responsibilities of the IRB

IRBs should address at least four forms of COI during the review of human subject research:

(a) financial COI of investigators; (b) COI when the investigator is also responsible for the clinical care of the patient/client; (c) COI when an IRB member has a proprietary interest in the sponsor of a project or product reviewed by the Board, and (d) COI when an IRB member is also an investigator on a project reviewed by the Board. My comments will specifically address the proposed guidance for COI when an investigator also has a proprietary interest in the sponsor of a project or a product reviewed by the Board.

The IRB is specifically mandated to review the adequacy of the protection of the rights and welfare of human research subjects and is the institutional body trained and responsible for ensuring full disclosure of research related matters to human subjects. The IRB conducts its review according to the federal regulations and the principles of The Belmont Report. The first principle of The Belmont Report is "respect for persons" or the recognition of the autonomy and dignity of potential subjects embodied in the right to full disclosure of information that may affect their willingness to participate in research. The IRB is ethically obligated to review research and ensure full and appropriate disclosure in the informed consent document of an investigator's financial interests that may affect a subject's decision to participate in the research. In order to meet the letter and spirit of the ethical guidelines, the IRB must have sufficient information to assess an investigator's financial relationship with a sponsor in order to analyze and determine the adequacy of the disclosure in the consent document.

Complete Information Provided to the IRB One should question the wisdom of suggesting that a COI committee has sufficient expertise or training to determine the adequacy of the content or nature of a research informed consent process or document. Managing, or avoiding, real or perceived potential conflicts of interest, for the institution and the investigator, is not the same as ensuring complete disclosure of information that may be pertinent to a subject's decision about whether to volunteer for research. Such a charge is clearly outside of their training, purview, or mandate. Furthermore, the guidance document suggests that the COI committee would only share "problematic" findings with the IRB. The guidance document, however, does not delineate the nature or scope of "problematic" findings.

I submit that the IRB is the most qualified to consider, after reviewing complete documentation, whether subjects should be informed of such conflicts and the nature of the disclosure. After all, the IRB is mandated to address such issues, i.e., disclosure of the purpose, procedures, risks, benefits, and alternatives to research, on a day-to-day basis. Additionally, Federal regulations and ethical guidelines require that the IRB ensure that subjects receive sufficient information to make a considered decision about whether to participate in research. Only one institutional administrative committee has ultimate authority and responsibility for the content of such disclosure. That committee is the IRB. Their responsibility cannot be delegated to another institutional body. Yet, the proposed guidance document suggests that another committee determine the extent and nature of information provided to the IRB, thus pre-empting the Board's ability to make a considered decision regarding whether a research subject should be informed about a potential conflict.

If the disclosure of a financial relationship in clinical research to subjects is of sufficient importance to warrant policy guidance, it is clearly a mandate for the IRB to review and consider the nature of such disclosure to subjects. A COI committee or an institutional official responsible for conflict of interest should not be burdened with the responsibility of determining when an investigator's positive disclosure warrants review by an IRB. Ultimately, providing an IRB only with what is deemed as "problematic" disclosures impedes the Board's ability to independently review the information and ensure appropriate informed consent regardless of the determination of other institutional bodies. A parallel situation would be a Vice President for Research determining that an IRB should only receive the informed consent document for review unless s/he determined the research was "problematic" enough to warrant their review of a complete scientific protocol.

An additional page or two of information will not add considerably to the IRB workload while ensuring discussion of the content of such disclosure in the consent document. Such disclosure ensures that we uphold the dignity of the subject through the time-honored process of IRB review.

I encourage DHHS to revise the guidance document to ensure the protection of the rights and welfare of human research subjects by prompting institutions to provide IRBs with complete information to determine the adequacy of disclosure of all investigator's possible COI, regardless of the "problematic" nature of the information. As Associate Provost C. K. Gunsalus, University of Illinois at Urbana-Champaign, observed on disclosing potential conflicts of interest, "The best practice is for there to be disclosure. If it didn't influence you, why is it a problem to disclose it?"

Thank you for considering the late submission of my comments. My comments do not necessarily reflect the opinions of my employer, the University of California, and should not be cited as such.

Sincerely, Steven Peckman
Associate Director-Human Subjects Research
Office for Protection of Research Subjects
University of California, Los Angeles