

Stuart Nightingale, M.D.
Office of the Assistant Secretary for Planning and Evaluation
Hubert H. Humphrey Bldg., Room 447D
200 Independence Ave., S.W.
Washington, D.C. 20201

9/28/00

Dear Dr. Nightingale:

Comments:

1. For each group listed below, what types of financial interests are associated with human subjects research funded or regulated by HHS agencies?

Clinical investigators (including sponsor/investigators)

Salaries as consultants, future income as potential employees, value of stock options, stipends for patient recruitment, stipends for research fellows, grants for research expenses, travel, meals, honoraria for talks

IRB members and staff

They should not have any financial interest in companies or products except by chance, and should clearly recuse themselves if they do. Commercial IRB's which owe their existence to company payment, and staff indirectly employed by companies doing research do have a serious conflict.

Awardee institutions

Institutions have a financial interest in their investigators earning grants, doing clinical trials, getting patents, paying for their research space, and incidentally, in writing papers. In some cases, institutions own stock in companies owned or run by their research faculty. I'm not partial to that.

2. Is there empirical evidence that informing research participants about financial relationships or financial conflict of interest of the investigator, the institution, or the IRB:

Can cause or prevent real or perceived harm (physical or psychological) to human research subjects?

I am not aware of any studies of this kind; I doubt if informing people would hurt them or protect them from known harm. Totally irresponsible research would probably have just as much chance of being done and harming people as good clinical trials.

Can compromise the objectivity of the associated research?

Informing participants should in no way affect the objectivity of the resesarch adversely.

Can adversely or positively affect participation in the trial?

Most definitely, but I don't know empirical evidence. Clearly participants will be more reluctant to take part in a trial, or to take part with full cooperation, if they are aware of the conflict of interest of the investigator or the institution. The IRB is a bit removed from this relationship. Unfortunately, I do not know any obvious remedy for this negative effect; I think it is one of the costs of honesty.

Can enhance the informed consent process by more fully informing potential participants?

I can't picture an empirical study on this! Enhancing informed consent? Judged how? One tries to give potential participants as much information as they are willing to absorb, which is often much less than the IRB wants you to give them. All information transmitted to the subject enhances informed consent, more or less by definition!

Can be understood by and is meaningful to the potential research participant?

People understand money. Empirical studies? I doubt anyone has done any. The full complexity of some interests is beyond what one can practically disclose, but the existence of financial interests would definitely be understandable.

3.If information about financial interests is disclosed to potential participants in clinical trials, what information should be disclosed and at what level of detail?

Should potential participants be told of all of the financial interests of investigators, IRB members, or institutions, or only those financial

interests which constitute a financial conflict of interest or might constitute a financial conflict of interest?

This must be a catch question, since the idea of revealing your entire financial life to a research participant is ludicrous. Of course, all relevant financial interests should be disclosed.

Should potential participants be told what protections are in place and are working to ensure that financial conflicts are managed, reduced, or

eliminated to promote objectivity and enhance human subject protection in the trial?

Yes, this would be useful, especially if something were really being done!

Are the financial limits set forth in current PHS regulations covering awardee institutions still appropriate for clinical researchers?

Yes, the specific amounts don't matter so much as starting a review process.

What are appropriate levels of reportable financial relationships for IRB members and institutions?

As I indicated above, IRB members should have no financial interests in the research they are reviewing.

4.If information about financial interests is disclosed to potential participants, when and how should information about financial conflict of interest be provided to them?

It should be part of the oral explanation that the researcher gives to the potential participant, and the consent form should allude to the fact that disclosure has occurred. I would not put a huge amount of detail in the consent, which most subjects are reluctant to read fully.

If information about financial interests/conflict of interest involving institutions, IRBs, and investigators should be provided, what is the optimal point in the process for disclosure?

Before the participation of that person starts! Note that if there is a strong motivation for the individual to participate (opportunity to get free medicine, for example), this disclosure may be simply ignored.

Should information be provided by the institution, the research investigator, the IRB, or a third party?

I believe that the investigator should explain his/her interest.

Should disclosure information and institutional policy be provided in the informed consent document or in an entirely separate document?

As I mentioned, it should be referenced in the informed consent document; if it is very complicated, it would not be unreasonable to have a separate declaration, which is referred to in the consent form.

5. What are appropriate roles for the institution, the IRB, the clinical investigator (including sponsor/investigators), and perhaps other entities in dealing with financial interests or financial conflict of interest?

What are the responsibilities and obligations of each entity?

In our institution the IRB checks that the investigator has been cleared by the conflict of interest committee. It undertakes no investigation itself. The C of I staff is provided by the institution to monitor faculty outside interests, and does a reasonable job of detecting but an inadequate job of providing monitoring or followup. The institution must provide oversight, demand disclosure of financial conflicts, then insist on proper disclosure to research subjects, meeting attendees, journal editors, etc., figure out a way to monitor compliance, and have penalties declared in advance for violations of its policies. The clinical investigator should willingly comply with institutional policies for self protection as well as to protect research subjects. Institutional policies should not attempt to deprive the investigator of the fruits of discovery and development before commercialization.

How should each entity relate to the other entities?

Courteously. Seriously---information should be freely exchanged.

Should disclosed information on which determinations are made (including deliberations) be shared with the other entities? If so, what information should be shared and how and when should the disclosures be conducted?

The other entities entitled to know about conflicts besides those listed above would certainly include the investigator's department chair and dean. Ideally, the statements to the institution should go through them, but the committees might also contact them if decisions are made that involve monitoring activities or denying research privileges.

What confidentiality protections are/should be in place to safeguard the privacy and confidentiality of the investigator, IRB member, and institution?

I think that the privacy of the investigator is going to take a hit in this process. If everyone from his department chair to the faculty on the institutional committee on conflicts or the IRB (depending on the institution's policies) know about the conflict, it is hardly confidential. I would regard that as the cost of doing research with public participation and having financial interests outside the institution. On the whole, there is too much secrecy around. The institution also must risk something for its privileged position, in which it may profit from private arrangements.

6. Other than those at the Federal level, what protections exist to ensure that the financial conflicts are managed, reduced, or eliminated to promote objectivity in the trial and to enhance human subjects protection?

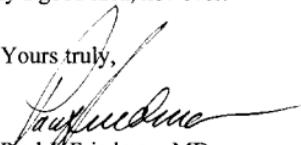
There are checks at the research approval stage in the institution, if it is motivated to make use of them. It is all too easy to just let things ride. It is not possible to eliminate a conflict without eliminating the faculty member's role in the research. Participation by faculty on monitoring committees is our policy for most difficult situations but I don't think it works all that well. It is quite difficult to deal with an investigator who is disingenuous, disorganized, or simply indignant. And it should take more time than a voluntary faculty member can spare!

Having the monitors check patient enrollment in projects could be very useful in keeping people honest or objective.

Protection of human subjects is the job of the IRB, rather than the financial/research monitoring committee, and its formal interest is already well established. As brought out in recent new items, IRB's tend to be too overworked to do a good job with their present charge. They need to be made stronger and receive adequate subsidy from the institution. This is one area where even the exceedingly well-motivated people who serve on the IRB may not be effective enough; the other agents require a little more motivation perhaps.

I hope these remarks get to you within your period of consideration. I'm not sure how they would be translated into regulations; I don't think that a lot of regulation is very productive. Very firm regulation of independent IRB's is probably a good idea, however.

Yours truly,



Paul S. Friedman, MD
Professor of Radiology
UCSD School of Medicine
200 West Arbor Drive
San Diego, CA 92103-8756