

September 29, 2000

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

Dear Dr. Nightingale:

In our capacities as President of the Federation of American Societies for Experimental Biology (FASEB) and Chair of the FASEB Science Policy Committee, we submit the comments below in response to questions posed in the July 3, 2000 *Federal Register* regarding financial conflicts of interest and human subjects protection. FASEB is comprised of 21 life science research organizations with over 60,000 members among its ranks. Our members represent over half of the National Institutes of Health awardees, and thus form an active contingent of the biomedical research community to which this issue and its ramifications are so critical.

Before delving into the specifics of this discussion, we would like to emphasize two points. First, we believe that the overwhelming majority of our colleagues diligently strive to maintain the objectivity and integrity of their investigations. Second, we believe that in order to encourage the translation of fundamental discoveries into novel modalities of patient care, some degree of financial conflict of interest is to be expected. This is not to deny the significant threat financial and other conflicts pose to research objectivity, nor to obscure examples of demonstrated misconduct, but to clarify that we must endeavor to build a system that is constructive, not restrictive. The public must be assured that their physicians and research institutions maintain patient protection at the core of their mission. The public must also be confident that the knowledge gained through federally funded research is broadly disseminated and made accessible to health care providers through the marketplace. The speed with which our past research success enables us to pursue today's scientific opportunities only reinforces the need to be vigilant in our partnership with the public.

The federal government, as guardian of its citizens' interests and safety, must ensure that all research is carried out in an ethical and productive manner. In so doing, it must also consider the culture of the research enterprise and the relationships underpinning its success. These relationships, specifically those between institution and government and between institution and its community, have provided practical oversight with the flexibility to develop customized infrastructure to best serve all parties' needs. Therefore, prescriptive federal regulations regarding financial conflicts of interest will not be the most effective solution to contain and resolve potential problems in the system.

Nevertheless, FASEB does support the development of federal guidelines, not regulations, to assist universities and other organizations in designing rigorous and locally appropriate policies. This would

facilitate the most effective interpretation and management of the multifaceted challenges presented to IRBs and investigators as they carry out their respective duties. Conscientious guidelines will provide a framework upon which institutional policies can be built and adapted to incorporate local cultures and concerns. It is the ultimate obligation of institutions to craft the specific procedures and regulations for their faculty and committees. FASEB applauds the initiatives within the community already underway to assess common challenges in dealing with conflicts of interest in any form. We welcome the opportunity to participate in the development of best practices that serve institutions, investigators, government overseers and most significantly, the individual participants in clinical trials.

Further, we would like to echo Dr. Koski's statement made at the conclusion of the August meeting, to say that we must look beyond discrete issues of financial conflicts of interest and focus on addressing the larger matter of preserving research integrity. Research integrity is not conceivable without sound protections for human research subjects. We must examine our mechanisms to preserve this integrity within the context of the rapidly changing landscape of education, health care, basic research and biotechnology.

#### Types of financial interests representing conflicts:

Conflicts of interest have the potential to directly affect the design, execution or interpretation of any study. Distinguishing between real and perceived financial conflicts, however, is difficult even with direct relationships of cash payments, equity holdings, or research support. The "value" of these relationships is based on the context of each individual situation. In some instances, such as "finder's fees" paid to investigators for each patient enrolled, the conflict is obvious and unacceptable in any clinical research setting and demands explicit disclosure. In others, such as personal stock holdings, investments in a small biotechnology firm may carry different risk levels than equivalent investments in a large pharmaceutical company; thus, the resulting potential for conflict may vary significantly. It should further be recognized that different types of financial conflicts relate differently to the structure of science. The value of equity in a biotechnology company can change dramatically in response to short-term developments regardless of the quality of the science, whereas the value of patent/licensing arrangements evolves with the science over a longer time. In addition, while the greatest emphasis often is placed on financial conflicts, it must be recognized that not all potentially harmful conflicts are financial in nature. Many of the "rewards" to scientists in their careers, be it a grant, specific compensation or recognition within a particular field, come as a direct result of the data produced in their laboratory. Therefore, the pressure to achieve experimental milestones is intense and multilateral. Although monetary gain is commonly the most visible and understandable conflict in the public eye, guidelines and policies designed to manage research conflicts must not deal with any one form to the exclusion of others, and we, as investigators, must remain mindful of them all.

Complicating the possible relationships discussed above, an increasingly prevalent and delicate instance of potential investigator conflict of interest is presented by researchers pursuing their own biological "inventions." In these cases, even a comprehensive, transparent oversight mechanism may not sufficiently clarify policies to dictate definitive courses of action for every situation. While patient protection must remain paramount, the end goal of translating fundamental science into medical

advancements is not well served by absolute regulations that cannot be adapted to individual circumstances where ideal alternatives, such as another investigator performing the study, are not practical. This is a testament to the need for institutional authority to implement common principles so that as the research community evolves to incorporate new partners and strategies, human subject safety and scientific progress are concurrently achieved.

Institutional IRBs present potential conflicts in two forms: that of an individual committee member and that of an institutional body. Many members of IRBs are clinical investigators and therefore subject to the same pressures discussed above. Furthermore, with the expansion of the technology sector of our economy, any member of an IRB is a potential investor in a biotechnology or pharmaceutical company that may be a research sponsor. IRB members should be subject to the same institutional conflict of interest policies as the investigators and staff on the protocols they review. They should recuse themselves from consideration of any study to which they are connected directly or indirectly, thereby obviating any potential for conflict.

It has been suggested that there may be inherent conflicts of interest for IRB members and administrators employed by the institutions that they are monitoring. FASEB believes that with appropriate institutional infrastructure and support, IRBs can – and do – remain isolated from specific institutional concerns, such as specific investments in potential studies and/or study sponsors. This is an issue that should be articulated by the institutional community as it develops best practices for enhancing IRB function and effectiveness.

In contrast, commercial IRBs have direct potential for conflict that necessitates thorough exploration. Whereas academic IRB committees can be largely insulated from the financial dealings of their home institutions, for-profit IRBs exist to serve their client's needs, i.e. clinical research sponsors. FASEB acknowledges that this business orientation does not inevitably confer sub-standard ethical practices and that similar potential for breaches is found in academic environments. However, commercial IRBs proximity to financial pressures increases the risk for conflict to affect operating procedures. Therefore, as a community, we must carefully examine the basis and ramifications of the shift in the percentage of clinical research studies performed in the private sector so that research volunteers are equally protected in every venue.

With the expansion of licensing agreements, stock options and other financial linkage with research companies, institutions are faced more frequently with possible financial conflicts of interest. The potential of these conflicts to introduce bias are still being identified and explored. The increasing percentage of non-federally sponsored research carried out at academic centers requires adaptation and innovation to preserve the traditional academic missions under a new milieu of circumstances. FASEB commends the on-going efforts of the Association of American Universities to confront the difficult questions posed by these changing circumstances and to develop self-guidance tools to harmoniously achieve all of their goals, including responsibilities to local constituents.

Empirical evidence of the effect of financial conflict disclosure on study participation:

Unfortunately, there is an absence of formal studies of the impact of disclosing conflicts of interest, financial or otherwise, on the willingness of subjects to enroll in clinical protocols. The anecdotal essence of the available information on this critical issue reinforces its ethical complexity. While it is difficult to believe that the disclosure of investigator or institutional financial conflicts of interest with specific studies would not influence the decision process of participants, it is not possible to provide truly informed consent without doing so. The paramount concern throughout the process of clinical research must be the ethical conduct of each study, which is predicated by informed consent.

#### Information disclosure to potential participants:

The complexity of conceivable situations and audiences reiterates the need for local oversight of financial conflicts of interest, based upon common principles, to define the specific language and extent of disclosure to volunteers. The underlying mechanism for disclosure must be transparent, subject to public scrutiny and provide information that is meaningful to the participant. Potential subjects should be informed that there is an institutional policy governing potential investigator and staff financial conflicts of interest and that there is a designated individual for any questions that may arise (see next section). Verbal enumeration of the general protections in place is not likely to be helpful to patients or their families focused on specific studies, and therefore FASEB suggests that a separate document, written in lay terms, be used to provide patients with basic information that could be reviewed at any point in time.

In general, FASEB believes that the details of disclosure should vary according to the nature of the conflict and be directed to the subject's contextual perspective. Federal guidelines would serve to assist IRBs and investigators in crafting appropriate disclosures and would heighten awareness of certain types of conflict and the appropriate questions to be asked when seeking to manage them. Personal compensation to investigators for executing studies or enrolling patients, for example, would clearly merit explicit disclosure, whereas research support (especially in instances of investigator-initiated studies) to an investigator's laboratory cannot be accurately conveyed through a simple dollar figure. In these cases, it may be most appropriate to inform potential subjects only of the existence of a financial relationship and remind them of their access to an independent party (see below) should they have any questions or concerns. This form of general disclosure is also appropriate in cases of institutional holdings or other financial relationships. Nevertheless, as alliances between academia and industry continue to grow in number and complexity, this difficult question will call for frequent review.

Regarding the appropriateness of PHS regulations for clinical research at awardee institutions, FASEB recommends that they be modified to incorporate the informed consent process. Current language merely defines conflicts of interest that are to be "managed, reduced or eliminated." As detailed above, FASEB proposes that any guidelines or regulations should include appropriate disclosure of any potential conflicts deemed relevant through institutional review. With respect to federal "limits" or "levels" of financial relationships, FASEB believes that static dollar figures do not account for the fluid nature of these relationships and again indicate the need for local interpretation.

### When and how to provide disclosure:

For the benefit of the participant, FASEB feels conflict of interest disclosure, with respect to the investigator and/or the institution, would be most suitably placed within the informed consent document. The protocol-designated individual responsible for obtaining subject consent should specifically highlight any disclosure information during the informed consent process. The prospect that this individual will not appropriately divulge financial conflicts is no greater than for any other potential protocol-associated risk factor. Standard language identifying a third-party to whom questions regarding financial conflicts of interest may be directed should be included in the informed consent document regardless of the existence of any disclosed conflict. Specification of the appropriate individual should be left to the institution, based on its internal mechanism to oversee conflicts of interest in human research studies. We recognize that informed consent is a continuous process, but refer, in this particular context, to the point when the protocol is reviewed and the informed consent document presented to the participant for consideration of the study.

### Appropriate roles in dealing with conflicts of interest:

Investigators, staff, IRBs, institutions and sponsors must all be open and forthcoming with respect to potential conflicts in general and on a project-by-project basis. Individual privacy concerns must also be integral to any federal or institutional policy and, thus, openness does not resolutely imply public disclosure. The policies, regulations and sanctions governing financial conflicts of interest must be transparent and subject to public scrutiny, but the details of individual's financial situations can be considered confidential by the university – excluding cases of direct and personal compensation for specific studies as discussed above. In the case of institutions, privacy is not an issue and therefore their obligation to the public demands disclosure of any circumstances that may be perceived as compromising study objectivity.

The intricate nature of possible financial relationships between individual investigators and the private sector warrants examination by a committee distinct from the IRB that has the focused task and specialized expertise to interpret the ramifications and risk for conflict. This committee and the IRB should act as partners with a clear means of evaluating potential conflicts of interest in human research studies. The IRB would preside over the issues directly pertaining to human subjects based upon the determination of any financial conflict by the Conflict of Interest Committee. Open and frequent dialog between the two committees is paramount to participant protection. The requisite level of dialog and flexibility to ensure that this system operates appropriately cannot be achieved through prescriptive federal regulations. FASEB encourages universities to seek out and share their best practices for establishing strong safeguards and reaffirms that flagrant and/or intentional violations of such policies are absolutely intolerable. Accordingly, provisions for due process must be included to uniformly protect both "whistle-blowers" and the accused. As scientists, public trust in the integrity of our work is fundamental and cannot be sacrificed or tainted.

### Existing non-federal protections:

Many universities and academic institutions have already created dedicated Conflict of Interest Committees that have promulgated stringent campus provisions guiding research practices. The federal role – to assure the public that substantial safeguards are operating at every institution – would therefore not be best served by dictating specific mechanisms to manage potential conflicts of interest in human research. Rather, FASEB believes that federal guidelines in this area would provide useful standards of practice from which institutions could build locally appropriate policies. We do not believe that these guidelines would become a minimum standard for protection of human research subjects, since institutions must guarantee the safety of their community patients if they are to achieve their broader goals.

In closing, FASEB maintains that the demand for objective and high-quality data throughout the scientific process significantly counters the pressure to sacrifice research integrity for financial or other gain. It does not eliminate the possibility, but it reinforces the objective nature of research as a whole. This premise should underlie any effort to enhance the mechanisms governing conflicts of interest in human or any other avenue of research. FASEB appreciates this opportunity to voice its thoughts and welcomes further interactions in this regard among all relevant stakeholders. We stand ready to work with patients, their physicians, government agencies, and research institutions to ensure that the highest standards of conduct are maintained in human subjects research.

Respectfully yours on behalf of FASEB member societies,

Mary J.C. Hendrix, Ph.D.  
President

Sue P. Duckles, Ph.D.  
Chair, Science Policy Committee

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