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Association of Clinical
Research Professionals

June 2, 2003 03 JUN -3 A9:28

Dockets Management Branch (HFA-305)
Docket Number 02N-0475
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

To Whom It May Concern:

The Association of Clinical Research Professionals has prepared comments to the Draft Guidance on Financial Relationships and Interest in Research Involving Human Subjects published on March 31, 2003 at 68 Fed. Reg. 15456, Docket Number 02N-0475. Responses were due by Friday, May 30th, but we were unable to submit our response online as planned because the site only allowed for documents fewer than 4000 characters. I spoke with Glen Drew at the Office of Public Health and Science that day about the problem, and he instructed me to send the document to him via email, as well as send a hard copy.

The ACRP's response is enclosed. I do hope it will be reviewed and its contents considered before the Draft Guidance becomes final.

Thank you,

Katherine Madigan
Special Assistant to the CEO for Special Projects and Government Affairs
Association of Clinical Research Professionals

02N-0475 C21

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May 30, 2003

Dockets Management Branch (HFA-305)
Docket Number 02N-0475
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Draft "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection – Comments on Docket Number 02N-0475.

Dear Sirs:

The Association of Clinical Research Professionals (ACRP) appreciates the opportunity to comment on the Draft Guidance on Financial Relationships and Interest in Research Involving Human Subjects ("DG") published on March 31, 2003 at 68 Fed. Reg. 15456. The ACRP is a diverse network of clinical research professionals including clinical research coordinators, investigators, and associates, research and development project managers, regulatory affairs and compliance professionals and quality control and assurance auditors. Its membership spans fifty-two countries and includes over 17,000 members. Founded in 1976, it has a deep experience among its membership with the issues raised in the clinical trials process.

Fueled by the drive for enhanced integrity and objectivity throughout the research process, and the needed collaboration between medical research participants and industry, the role of financial relationships in the process is an important topic for all of the

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interested parties to address. As a result, we welcome and appreciate the opportunity you have provided to do so.

I. **The Use of Guidance In The Process**

You have asked for comment on the Guidance in general. ACRP believes that the Guidance is helpful in calling attention to the issues it raises. There are, however, a number of concerns which ACRP recommends could be addressed prior to it becoming final.

First, the approaches intimated by the DG seem to be primarily based upon an academic medical center (AMC) model and structure for the conduct of research. Through its approaches to the issues raised, it does not address the structures or options that might exist where independent investigators or structures are involved that are not centered around an "institution" or there is not an "institutional official" readily available. Indeed, to address such situations, it may well be much more useful to develop express rules with respect to the definition of conflicts, than to merely publish Guidance which offers issues, but no real Guidance with respect to how to resolve conflicts in non-institutional settings.

Second, notwithstanding the comment that the Guidance does not change or impose any new requirements, we note the DG actually states that "A Financial interest related to a research study may be a conflicting financial interest if it will, or may be reasonably expected to, create a bias stemming from that financial interest." (Emphasis added.) This statement, which actually intimates a definition, suffers from a number of deficiencies. First, it lacks clarity as to those interests that actually are, as opposed to may be, conflicts that must be managed or resolved. Second, it fails to provide any insight into what circumstances would illustrate those situations where there is a financial

interest that would create a bias, but would not be deemed conflicting and, at a minimum, require disclosure and management.

Third, the DG fails to address the role that non-governmental sponsors or other involved third parties may, and should play in the process of identifying and managing conflicts. In this regard, the OIG's recent solicitation of comments with respect to a potential exception to the prohibition on inducements to Medicare and Medicaid beneficiaries in certain clinical trials indicated circumstances where private suppliers may play a role in government sponsored trials [67 Fed. Reg. 72892]. A question also exists as to whether conflict of interest rules and standards should be different for governmental as opposed to privately sponsored research.

Fourth, the DG fails to indicate whether separate approaches and standards should be considered for different types of research. For example, the implications of financial interests on basic science research as opposed to clinical trials research, or records review as opposed to testing of a specific drug or treatment regimen are vastly different.

Finally, ACRP believes the final Guidance should recognize explicitly both that the risks inherent in conflicts of interest in research are not limited to financial conflicts, and that such conflicts must also be addressed and resolved.

II. Non-Governmental Approaches To Conflicts

To comment on each of the approaches, recommendations, and comments articulated by the various cited non-Federal publications would be a significant task requiring additional time. If concepts or recommendations set forth in the materials are likely to be put forth in policy statements or as part of the Guidance, ACRP strongly suggests additional time for comment, be extended and a specific focus be provided as to those elements of most interest to the Secretary.

ACRP would, however, offer the following comments on the AAMC approach. First, it does not believe that the AAMC approach with respect to a wide range of financial interests that there is a rebuttable presumption that absent compelling circumstances and a plan for managing conflicts research should not be conducted either at or under the auspices of the institution is necessary or appropriate (See Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of An Institution's Financial Interests In Human Subjects Research, October 2002, p. 10). Where there has been necessary and adequate disclosure of a conflicting financial interest, a plan to manage that conflict and implementation of that plan, the presumption urged by AAMC is not necessary, and likely to be counterproductive. In addition, it may well lead to an uneven playing field between Institutions where conflicted research can often be assigned or directed within the same academic team or department.

Second, ACRP believes the Secretary should both specifically identify and formally endorse the ethical opinions with respect to conflict management established by the American Medical Association, specifically as articulated in Opinions E-8.0315 Managing Conflicts of Interest in the Conduct of Clinical Trials; and E-8.031 Conflicts of Interest: Biomedical Research.

III. Guidance for Institutions, IRBs and Investigators

A. General Approaches to Address Financial Relationships and Interests ("General Approaches")

ACRP supports a flexible approach to dealing with financial conflicts on a organizational level and the demonstrated avoidance of a "one size fits all"

approach. Consistent with that philosophy, ACRP offers the following comments on the General Approaches:

1. There is no level at which a financial conflict, as defined, would not conflict if it has the potential to create a bias. This is the case for even which might be perceived as insignificant financial interests, e.g. equity interests less than 5% (see 42 CFR 50.603; 45 CFR 94.3). The issue is more realistically at what level such risks must be managed or eliminated. Hence the question "At what levels could [financial] interests cause potential or actual conflicts" should be restated to better read, "At what levels should financial interests be required to be managed or eliminated?"
2. The General Approach questions should be expanded by adding –
   a. What interests or entities need to be participants in developing a conflict of interest policy; and
   b. What role should sponsors or other third parties play in addressing conflicts of interest as they arise?

B. Points for Consideration

ACRP agrees that financial interests may be managed and that a variety of methods or combinations may be effective. It is noted that more efforts may be prior to or during the conduct research. Not mentioned, but in some cases also effective, may be efforts after the research, but prior to conclusion or publication of the results, for example, by an independent data review or analysis.

With respect to the remainder of the items identified in this portion of the DG, ACRP's comments are as follows:

1. It would be helpful to receive guidance on what issues the Secretary believes needs to be explored in ascertaining whether given the financial relationships involved, the institution or practice site, is an appropriate site for the research; and
2. Whether, as noted above, the Secretary believes the risks posed by certain types of research, e.g., basic science or post-mortem record reviews, merit a different level of concern than clinical trials.

C. Specific Issues For Consideration

1. Institutions

As previously noted, the Guidance should formally recognize that aspect of clinical research take place outside "Institutions" and that flexible approaches to management are appropriate in those other settings provided the goals of financial conflict resolution are met. In addition, ACRP believes that:

(a) The use of independent organizations to hold or administer the Institution's (entity's) financial interests will not always be required. Instead, clear separation between those managing financial interests and those responsible for the conduct of research is adequate, particularly in non-clinical trial research; and

(b) In establishing its conflicts policies, the institution should receive the input of all the concerned constituencies, including sponsors.

2. Investigators

Although the Guidance is limited to financial interests, ACRP believes it is important for investigators to assess conflicts of interest whether they or financial conflicts arise in other contexts. As a result, financial conflicts,

while deserving emphasis, should not be emphasized to the exclusion of other conflicts.

Second, as previously noted, ACRP endorses the ethical approaches to financial conflicts articulated by the AMA. As a result, the disclosure of significant compromised financial relationships should not be discretionary, as is potentially allowed by the Guidance. It is better to have a clear rule and a level playing field in this regard.

IV. **Conclusion**

ACRP believes that the Guidance is a useful step in what is clearly an ongoing process. As a result, ACRP believes the Guidance should formally state that it should be distributed to all IRB members, investigators, and the chief administrative officer within an organization responsible for oversight of the research operations, as well as the Chief Executive Officer and Board members. This will have the positive effect of placing before all the concerned parties within the organization a strong statement of the importance of addressing financial conflicts of interest, as well as the important issues to consider in doing so.

Yours truly,

Thomas L. Adams, CAE
Chief Executive Officer