ACRO

May 21, 2003

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 Interests in Research Involving Human Subjects: Guidance for Human Subject Protection"

Dear Sirs:

The Association of Clinical Research Organizations (ACRO) applauds Secretary of Health and Human Services (HHS) Tommy Thompson for the issuance of the above-referenced draft guidance document on March 31, 2003, and is pleased to submit the following comments.

Today, clinical research organizations (CROs) assist pharmaceutical, biotechnology and medical device companies with the conduct of thousands of clinical trials each year, and are a key participant in the development of new drugs and new treatments. In fact, well over half of pharmaceutical company research and development (R&D) expenditures fund studies run by CROs. Members of ACRO include Covance Inc., Kendle International Inc., PAREXEL International Corp., PPD, Quintiles Transnational Corp., PharmaNet LLC, DermTech International, Ingenix, Lineberry Research Associates, Medifacts International, Omnicare Clinical Research and PRA International. These companies employ more than 40,000 people worldwide, conduct research in 60 countries, and represent a multibillion-dollar industry.

For ACRO member companies, the safety of human participants in clinical research is a core issue, and we are aware that financial or other considerations may 'color' the design, review, approval, conduct, monitoring, analysis or reporting of research conducted by or under the auspices of an individual, institution, or other non-profit or for-profit entity. ACRO supports the definition suggested in the draft guidance, that "a financial interest related to a research study may be a conflicting interest if it will, or may be reasonably expected to, create a bias stemming from that financial interest," and agrees that such conflicting financial interests cannot be allowed to adversely affect the rights and welfare of human subjects in research.

ACRO thanks HHS for the consultative spirit in which this draft guidance has been offered, and appreciates that it does not propose to change any existing regulations or requirements or impose any new requirements relating to financial interests in research. At the same time, we do want to note that in outlining a series of "points for consideration" and "specific issues for consideration", the draft guidance addresses itself to "IRBs, institutions engaged in research, and investigators"

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exclusively – an approach that may forego the opportunity to stimulate new thoughtfulness about potential financial conflicts across the broader spectrum of participants in today's complex research environment, including (Federal and commercial) sponsors, CROs, SMOs (site management organizations,) and others.

CROs provide a wide range of research and development services to industry sponsors, including assisting in the creation and/or implementation of the clinical study budget, which is key to defining financial relationships between and among sponsors, investigators and others in such a way that financial interests will not adversely affect the rights and welfare of study participants. In regard to payments made to investigators and institutions, ACRO endorses the principle articulated by the Pharmaceutical Research and Manufacturers of America (PhRMA), "Payment made to clinical investigators or their institutions should be reasonable and based on work performed by the investigator and the investigator's staff, not on any other considerations." [1]

We note that the draft guidance "does not address HHS Public Health Service regulatory requirements that cover institutional management of the financial interests of individual investigators who conduct PHS supported research." Nor does it address "FDA regulatory requirements that place responsibilities on sponsors to disclose certain financial interest of investigators to FDA in marketing applications." Currently, investigators involved in FDA-regulated research certify to a sponsor (under 21 CFR 54.4) the absence of significant financial interests [FDA form 3454] or disclose such significant financial interests [FDA form 3455], whereas PHS-funded investigators report their significant financial interests only to their home institutions, which then must "manage, reduce, or eliminate" conflicts, and later report on those efforts to the funding source. While we cannot comment on the effectiveness of the institutional management approach, the experience of ACRO members suggests that requiring disclosure of financial interests to the sponsor, with subsequent review by a regulatory agency that can, in fact, reject data that may have negatively affected the integrity of a study serves as a powerful mechanism to discourage the use of investigators who hold significant financial interests in a product.

In the section entitled "Guidance for Institutions, IRBs and Investigators", under B. "Points for Consideration" the draft suggests that each of these entities should consider a series of questions, including "What interests are created by the financial relationships involved in the situation?" In general, ACRO supports the kinds of inquiries into financial interests suggested under this question. However, we are concerned that one of the suggested inquiries may confuse several different issues and asks IRBs, institutions and investigators to make a determination for which there is little basis.

The question is – Do individuals or institutions involved in the research "receive payment per participant or incentive payments, and are those payments within the norm?" First, this suggested question confuses two issues: the use of incentive payments, and utilization of a clinical study budget that is calculated based on the costs of the study per human participant. ACRO acknowledges that the use of incentives, especially as those would relate to the number of subjects enrolled in a study can be problematic, and if utilized at all must be structured with great care. On the other hand, calculation of study budgets based on per participant costs is a standard practice in commercially-sponsored research. Simply, sponsors of FDA-regulated studies rarely,

[1] See: "Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results", PhRMA, June 2002 – which also require that "payments or compensation of any sort should not be tied to the outcome of clinical trials", and prohibit direct ownership interests by clinical investigators or their immediate family, or compensation for work in company stock or stock options.

if ever, provide a total upfront grant for an estimated number of subjects, as may occur with NIH and other federal grants. Further, the use of per participant budgeting provides a level of transparency regarding the financing of a study that is far better than that offered by the direct costs-indirect cost rate (including institution 'facilities and administration') grant model used for federally-funded studies. Finally, unless the suggested question is careful to clarify that institutions, IRBs and investigators consider "per participant" payments exclusive of the costs of conducting the study,[2] this inquiry cannot produce any meaningful data, since the IRB, institution or investigator would have no way of distinguishing the 'norms' for a study in which the actual cost of clinical procedures is $1,500 per subject versus those for a study in which such actual costs are $25,000 per subject. We suggest, then, that this suggested query be modified to read, "Do individuals or institutions involved in the research – *receive incentive payments, and could those payments affect the rights and welfare of the subjects*?"

Since its inception, ACRO has strongly advocated for the development of uniform human research subject protection requirements that would apply to all research subject to Federal oversight, regardless of the source of funding for the research or the site where the research is conducted. Again, we applaud the Department of Health and Human Services (HHS) for issuing this draft guidance and appreciate its encouragement of greater consideration of financial relationships and interests in research. We believe that all participants in the research environment must be fully committed to the protection of research participants, and fostering a better awareness of the impact, or potential impact, of financial interests on the rights and welfare of human subjects will support that commitment.

On behalf of the leading clinical research organizations that are members of the Association of Clinical Research Organizations (ACRO), I am pleased to submit these comments.

Sincerely,

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[2] See 21 CFR 54.2