September 25, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: Docket No. 2008D-0406: Information Sheet Guidance for Sponsors, Clinical Investigators, and Institutional Review Boards on Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

Dear Sir or Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research organizations (CROs). Providing specialized services to pharmaceutical, biotechnology and medical device companies in the U.S. and around the world, our member companies are integral to the clinical research enterprise and the development of new biomedical products.

ACRO applauds the FDA for issuing this draft Information Sheet Guidance, as it attempts to respond to recurring questions raised by sponsors, IRBs and, most importantly, clinical investigators regarding completion of a document (Form FDA 1572) that is key to insuring compliance with regulations relating to the conduct of a clinical investigation.

Our comments and suggestions regarding specific items in the FAQ format of the draft Information Sheet Guidance follow here:

Question #3: When must this form be completed and signed by an investigator?

- ACRO suggests that the agency expand this response to further clarify how FDA defines "before permitting an investigator to begin participation in a clinical study". We support the prerequisites cited, for instance, that the investigator understands the protocol and the investigator's brochure, is familiar with applicable regulations, etc. However, we are uncertain as to whether other activities, such as site initiation and subject pre-screening can precede signing of the Form FDA 1572. Can the agency elaborate on this issue? At a bare minimum, we would suggest that the investigator should

227 Massachusetts Avenue, NE, Suite 300, Washington, DC 20002
T 202 543 4018 F 202 543 5327 E info@acrohealth.org www.acrohealth.org
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complete and sign the 1572 prior to shipment of investigational product to the site.

- When a 1572 is signed in a Part 11 Compliant System can the 1572 with the electronic signature stand alone or does the FDA require other documentation to prove the authenticity of the signature?

Question #5: What are the minimum qualifications of an investigator?

- ACRO agrees that minimum qualifications of an investigator include familiarity with human subject protection requirements and GCP standards. In many instances investigators are provided basic instruction in applicable requirements during the Investigator Meeting. We suggest that FDA might expand upon this response to state the agency's expectations regarding the extent of training and documentation that should be created and maintained to support an investigator's familiarity with HSP and GCP requirements.
- While not specifically addressed in the Draft Guidance, ACRO would like to comment on the issue of investigator 'certification'. While we are strongly committed to improving the scientific and ethical knowledge of investigators and research staff, we are aware of no legislative or regulatory support for requiring investigator certification nor do we believe that it would be appropriate for the FDA to support certification, whether mandatory or voluntary, by asking on the 1572 whether an investigator has been trained or 'certified' by any particular organization. We believe the FDA should fully enforce the obligation of sponsors to select qualified investigators, but should neither require nor implicitly endorse 'certification' when the result of such an action will be to raise already high entry standards and, to give one example, limit participation of 'occasional' investigators, such as those engaged to participate in large observational studies conducted in the post-approval sphere.

Question #7: When must a 1572 be updated or a new 1572 completed and signed by the investigator to reflect new or changed information?

- ACRO agrees that changes in original information contained on the Form FDA 1572 may be adequately documented within study records. However, many sponsors ask investigators to complete a new Form FDA 1572 to document such changes. We believe that requiring the completion of new 1572s is confusing, duplicative and burdensome to all involved, and we suggest that the final Information Sheet Guidance recommend against this practice.

- One circumstance not addressed in the Draft which, in our view, requires a new Form FDA 1572 be completed is when the investigator at an investigative site changes. We recommend that the guidance be clear that in this instance the new investigator must complete and sign the Form FDA 1572.

Question #10: Must investigators who conduct studies outside of the United States sign a 1572?

- As the agency is aware, some foreign investigators refuse to sign a 1572 on the basis that they follow country-specific regulatory requirements and/or have been advised by a national regulatory authority not to agree to a legal requirement that is enforced by a foreign (U.S.) agency. In our experience, the requirement to sign a 1572 has been waived by the FDA on a case-by-case basis, presumably on the understanding that local requirements are equivalent to the regulations set forth at 21 CFR 312. We would appreciate additional guidance in regard to the list of regulatory equivalents that must be met in order for such a waiver to be approvable. Alternatively, the agency might consider developing a non-US investigator version of the Form FDA 1572.

Question #12: Must foreign clinical sites in a multinational study that includes domestic sites be conducted under an IND?

- ACRO appreciates the FDA's attention to questions surrounding foreign investigators. The last paragraph of this FAQ discusses the requirements to provide IND safety reports to investigators, but it is unclear whether foreign investigators not under the IND do or do not need to be sent safety reports.

Question #17: How should an investigator's name appear on the 1572?

- Because many revisions to the Form FDA 1572 have been requested because of the literal form in which an investigator's name was written, it would be helpful if FDA clarified its definition of "legal name". For example, should middle initials be used or the full name written out, should titles, degrees or other professional qualifications be included, etc.?

Question #18: What address should be entered into Block # 1?

- ACRO requests that the Information Sheet Guidance clarify the definition of "official address of record". For instance, some investigators set up separate business entities for their research practices with an address different from that of their clinical practice. Should the research address be listed even

though the sponsor might be aware that the investigator spends little or no time at that address? Would an FDA audit require that the CV address and study address match?

Question #24: What qualifies as a research facility for Block # 3?

- As an understanding of the necessary degree of specificity and granularity in the listing of "research facilities" is often a problem in practice, we would appreciate additional clarification here. For instance, if the investigator is located in a medical office building next to a hospital and see subjects in his office, but sends subjects to the hospital radiology department for a CT scan, is the hospital to be listed as a research facility? If a subject is sent to an outreach office of the central lab being used on a study for lab sample collection, is the lab office a research facility?
- Again, the increasing complexity of the research environment can make the definition of "research facility" difficult. To give another example, a study may begin in a hospital and then continue with the release of the subject to a secondary facility for long-term follow up, with data continuing to be collected and reported. In some cases, the identity of the follow up facility may not be known prospectively – can the agency clarify expectations regarding the listing of such secondary facilities and related monitoring expectations?

Question #26: As a convenience for study subjects, the protocol allows for daily injections to be administered by a registered nurse at each subject's home. Do subjects' home addresses need to be listed in Block # 3?

- Appreciating that the subjects' home addresses need not be listed, should the health care firm providing the nursing services be listed?

Question #27: What qualifies as a clinical laboratory facility for Block #4?

- If the study site is performing a CLIA waived test is it necessary to list the study site as a laboratory, e.g., if the study site performs an in-office urine pregnancy test? How about a more complex test such as an erythrocyte sedimentation rate?

Question #31: Should research nurses, other nurses, residents, fellows, office staff, or other hospital staff be listed in Block # 6?

- We believe that further clarification of subinvestigators to be listed in Block #6 is needed. For some studies conducted in a hospital setting, there may be

nursing staff on different shifts involved in routine care of subjects who also collect and chart data that may be reported on the CRF, e.g., AEs, or administering investigational product to the subject, but who are not direct members of the investigator's study team. Should these individuals be listed on the Form FDA 1572 or, simply, on study site documents, such as the staff delegation log?

- Would it be appropriate to relate the roles of staff to be listed in Block #6 to their roles in generating primary efficacy or safety data?

Question #32: Should pharmacists or research coordinators be listed in Block #6?

- Again, further clarification would be helpful. Should a research coordinator who primarily completes CRFs, but who may also query subjects regarding AEs or obtain vital signs during study visits be listed as a subinvestigator?

Question #33: Is a statement of qualifications required for subinvestigators?

- We agree that the statement of qualifications for subinvestigators is not needed for the purpose of providing that information to the IND. However, sponsors need to determine the qualifications of those individuals who may have a significant role in the trial. We recommend that FDA consider addressing within this FAQ the collection of CVs/statements of qualifications for the purpose of determining the training and experience qualifications of subinvestigators .

ACRO thanks the FDA for the opportunity to submit these comments, suggestions and requests for further clarification. Please do not hesitate to contact the Association at any time.

Sincerely,

Douglas Peddicord
Executive Director, ACRO

227 Massachusetts Avenue, NE, Suite 300, Washington, DC 20002
T 202 543 4018 F 202 543 5327 E info@acrohealth.org www.acrohealth.org

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