ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

July 19, 2021

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

Re: ACRO Comment Submission for—
Frequently Asked Questions — Statement of Investigator (Form FDA 1572) (Revision 1); Draft Information Sheet Guidance for Sponsors, Clinical Investigators, and Institutional Review Boards
Docket No. FDA– FDA–2008–D–0406

Dear Sir/Madam:

ACRO represents the world's leading clinical research and technology organizations. ACRO's member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices—from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance, and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide. With more than 200,000 employees engaged in research activities in 114 counties, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

ACRO thanks the FDA for developing an update to the *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)* to provide further clarification of FDA's thinking regarding waivers of the signature requirement on Form FDA 1572 for clinical trials conducted outside the USA under Investigational New Drug (IND) authority. ACRO welcomes the clarifications and flexibility that the update provides for foreign investigators who cannot sign Form 1572.

Specific comments on the text of the draft document are provided below. However, we believe it is important to recognize that requiring separate processes for IND/Non-IND non-US sites and Form 1572 signature waivers creates additional administrative burden for both sponsors and FDA, and potential delays to site activation. Clinical research today is increasingly focused on risk-based approaches to clinical trial management. FDA has acknowledged that the primary differences between ICH GCP and 21CFR 312 requirements are limited to the IEC vs. IRB constitution and investigator signature of the FDA 1572 form. Therefore, we would ask the FDA to consider whether the formal waiver process is still relevant. Rather than requiring applications for IRB and Form FDA 1572 signature waivers, we request the FDA to consider implementing a separate FDA 1572 form for non-US sites where language related to US IRB requirements is replaced with acceptance of an ICH E6-compliant independent ethics committee and where the investigator signs to confirm compliance with the protocol, GCP, and local regulations -- but omits reference to 21CFR. Such a process would have the additional benefit of mitigating the potential issue regarding versioning and date of information when an unsigned Form FDA 1572 is submitted.

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The following specific comments on the draft document have been raised by ACRO's member companies:

Page 4, lines 144 – 146 "A waiver request is required to contain at least one of the following (21 CFR 312.10(a)): 3. The reason(s) each investigator cannot or will not sign Form FDA 1572": In order to reduce the administrative burden on both the sponsor and the FDA, we recommend that it should be possible to consolidate waiver requests for sites in a particular country/region under a single rationale when the rationale is the same. Consequently, we recommend that the text is revised to read as follows: *"3. The reason(s) each investigator cannot or will not sign Form FDA 1572 which may be listed once in a single waiver request for all sites in a particular country, if applicable."*

Page 4, line 151 "Page 4, A waiver request is required to contain at least one of the following (21 CFR 312.10(a)): 5. Other information justifying a waiver": It would be helpful to include details of what other information, or examples of information, may be required. It has been the experience of some sponsors for the FDA to request translations of local GCP guidance and laws as part of the rationale for acceptability of a waiver when a site cannot or will not sign a waiver. Some institutions are unwilling to provide their policies for submission to FDA. And, while some countries may not have written policies or statements regarding the FDA 1572 form, it is well known by sponsors that many sites (for instance in European Union countries) cannot sign the form because of the approach taken by local regulators. We therefore recommend that the text should explain how these situations should be addressed.

Page 5 – lines 180-186 "Commitment by the sponsor to collect from each investigator for whom the signature requirement was waived, a completed but unsigned Form FDA 1572 that includes all information in sections 1 through 8 of Form FDA 1572 and a signed statement containing commitments equivalent to the commitments specified in Section 9 of Form FDA 1572. (Note: In place of Form FDA 1572, the sponsor may choose to use an appropriate alternative template of its choice.) (See the sponsor commitment example in the appendix.)": Member companies have created and utilized GCP statement forms for non-US sites for many years. These mirror the FDA 1572 form for sections 1-8 and then wording in the final section mirrors the wording in the 'investigator commitment' example in the FAQ. Rather than requiring an investigator to submit an unsigned FDA 1572 plus a GCP statement, we recommend FDA acceptance of a signed Sponsor-adapted combined form instead. Consequently, we recommend that the text is revised to read as follows: *"The sponsor may commit to collect from each investigator for whom the signature requirement was waived, a completed but unsigned Form FDA 1572 that includes all information in sections 1 through 8 of Form FDA 1572 and a signed statement containing commitments equivalent to the commitments specified in Section 9 of Form FDA 1572. (Note: In place of Form FDA 1572, the sponsor may choose to use an appropriate alternative template of its choice, incorporating the sponsor commitment example in the appendix. In this case the form would be signed by the investigator)."*
Additionally, where an unsigned FDA 1572 form is submitted with a signed statement of commitments, it would be helpful if the FAQ described how the form and the signed statement should be linked together, as this can be an issue during FDA GCP inspections.

Page 6, lines 212 – 216 "Does the sponsor need to wait for the waiver request to be granted before initiating the study at that site? Yes.":
We recommend that this answer be changed to read as follows:

> *"Yes, and the Agency will respond to the Sponsor's request within 30 days. If there is no response from the Agency within 30 days, it will constitute an automatic granting of the waiver."*

ACRO member companies have experienced delays of up to six months in approval of waiver requests. Such delay to site initiation is unreasonable when there are no specific issues that would prevent granting the waiver and all required local approvals to initiate the site are in place.

Page 8, line 167-173 "An alternative course of action could take the form of the submission of the following three items: Declaration by the sponsor that the regional (in the case of the European Union) or national regulatory authority is a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has implemented the ICH E6 Guideline for Good Clinical Practice.": Some countries where signing of the FDA 1572 form may not be permitted are not members of ICH and the FAQ document should therefore provide guidance on how the process should be managed in such countries. Additionally, a number of key territories for the conduct of international clinical trials are currently observers rather than full members of ICH (e.g., Israel, South Africa, Australia, Argentina, United Kingdom). We therefore recommend revising the proposed text to read as follows: *"An alternative course of action could take the form of the submission of the following three items: Declaration by the sponsor that the regional (in the case of the European Union) or national regulatory authority is a member or observer of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has implemented the ICH E6 Guideline for Good Clinical Practice."*

Page 9 – line item 331-336, item 7: "I will ensure that an IRB or an IEC that complies with the requirements of national and regional legislation and the Declaration of Helsinki, and that follows the recommendations in ICH E6, will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IEC all changes in research activity and all unanticipated problems involving risks to human subjects or others.": In some countries, especially in the European Union, the national regulatory authority has advised that it is not acceptable for local investigators to sign a form containing a similar statement to this because the clinical trial sponsor, rather than the investigator, is required to make the application to the independent ethics committee and/or reports non-compliance issues to the ethics committee. With the imminent implementation of the EU Clinical Trial Regulation and submission to ethics committees across the EU by the sponsor through a central portal, there may be further pushback across EU countries on this statement. Consequently, we recommend revising the required statement to read as follows: *"I will ensure that the site has received the required documents for the initial and continuing review and approvals of the clinical investigation(s) from an IRB or IEC that complies with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6."*

We recommend that the additions within the current document, when finalized, are consolidated with the text of the original 2010 Frequently Asked Questions – Statement of Investigator (Form FDA 1572) Information Sheet Guidance, rather than requiring sponsors to have to reference two closely related documents, which could potentially lead to errors.

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We also wish to take this opportunity to raise an issue related to the FDA's approach to flexibility with regard to inclusion of a foreign clinical study in an IND, which is described in an additional Frequency Asked Questions document published in 2012 - Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND, which states that *"A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND."* Despite this guidance directed to "Industry and FDA Staff", our member companies report that some FDA divisions continue to require that non-US sites are listed in the IND, thus limiting access to the flexibility that the guidance allows and, when coupled with delays in approving waivers, leads to unnecessary delay in the initiation of non-US sites. We acknowledge that this issue is slightly outside the topic of the revision on which comment is requested, but would like to take this opportunity to encourage FDA to ensure that all review divisions recognize the flexibility afforded to sponsors by current FDA guidance.

ACRO thanks the Agency for the opportunity to provide comments on this draft update to the Frequently Asked Questions – Statement of Investigator (Form FDA 1572).

Please do contact ACRO if we can provide additional details or answer any questions (knoonan@acrohealth.org).

Respectfully submitted,

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