

September 15, 2014

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

**RE: Docket No. FDA-2006-D-0031 – Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors
DRAFT GUIDANCE**

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 100,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

Each year, ACRO member companies conduct more than 11,000 clinical trials involving nearly two million research participants in 115 countries. On average, each of our member companies works with more than 500 research sponsors annually, and we have a broad and unique understanding of the roles, responsibilities and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards, clinical trial participants and ancillary providers of all types – that are part of the research enterprise.

Representing companies that routinely interact with IRBs, clinical investigators and sponsors, ACRO thanks the FDA for the above-referenced Draft Guidance, which explicates the Agency's latest thinking relating to the *informed consent* process and the obligations of IRBs, investigators and sponsors. While the Draft Guidance covers a broad range of issues, we will limit this brief comment to four topics that we believe could be further explored and developed before a Final Guidance is issued.

Section III, A, 3: Language Understandable to the Subject or the Representative

We thank the Agency for underscoring the number of adults who have basic, or below basic, health literacy and basic, or below basic, quantitative literacy – and the necessity to take these limitations into account when conveying information orally – during the consent

interview – and in the written informed consent form. In order to address the thorny issue of understandability and provide concrete examples of the satisfaction of the written component of understandability as required by 21 CFR 50.20, the Agency might consider soliciting from IRBs, sponsors and investigators examples of informed consent forms which the users believe are responsive to concerns regarding understandable language; understandable level; health literacy; and quantitative literacy. Further, the Agency might consider tasking the Clinical Trials Transformation Initiative (CTTI) with developing a template or templates of model informed consent form language, based on exemplary submissions. These templates could be posted for comment on the FDA’s web site, and perhaps incorporated as an Appendix to a Final Guidance.

Section III, E, 2: Alternative Methods of Obtaining Informed Consent

ACRO suggests that the Agency significantly expand this discussion in any Final Guidance to include the rapidly growing importance and role of mobile technology – iPhones, iPads, and apps – in the informed consent process. Because such new technologies can include electronic, interactive quizzes to assess understanding and comprehension, the Agency has missed an opportunity to not only examine more thoroughly various alternative, electronic methods of obtaining informed consent, *but also to examine how new technologies such as animated video, graphics, and interactive quizzes could simultaneously resolve some of the understandability and comprehension concerns discussed in III, A, 3 “Language Understandable to the Subject or the Representative.”* Preliminary research has indicated this may be the case.¹

Section IV, C, 1: Considerations for Multicenter Clinical Investigations

ACRO believes the Agency has missed an opportunity to discuss in this Draft Guidance the important role of central IRBs. In the one and only paragraph that mentions the concept of central IRBs, the Agency references the 2006 guidance “Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials” and states the following:

For multicenter clinical investigations, minor changes may need to be made to the consent form to address local and institutional requirements. When IRB review results in substantive modifications to the consent form, i.e. changes that affect the rights, safety, or welfare of the subjects, FDA recommends that the sponsor share the revisions with the investigators and their IRBs. If the clinical investigation has a central IRB working in cooperation with local IRBs, the revisions should be forwarded to the central IRB. Alternatively, local issues may be addressed by the central IRB depending on the review agreement between the local IRB(s) and central IRB.

When the IRB system was established in the 1970s, most research projects took place at a single site; today, however, it is common for research, including many clinical trials, to run concurrently at multiple sites, with perhaps 20 or 30 or 50 investigators and sub-investigators involved. Without central IRBs, ethical review becomes redundant and duplicative. Delays and resource costs are exacerbated when local review is repeated – and managed - over and over for a multi-site project. The job of IRBs is essential to the clinical trial process, ensuring the safety of patients and an ethical approach to study design. However, the variation in timelines for the same task among different IRBs and the redundancy – and thus added time and costs seen in multi-center studies – indicate there is room for improving efficiency in this part of the clinical trial process through a stronger recommendation for central IRBs.

¹ Rowbotham et al., [Interactive Informed Consent: Randomized Comparison with Paper Consent](#), March 6, 2013

Many stakeholders have raised and acknowledged the issue of IRB delays and redundancies numerous times. It has, in fact, been studied by the FDA, HHS's Office for Human Research Protections (OHRP), industry, private think tanks, and others since at least 2006, with a variety of recommendations being made to "encourage" use of central IRBs and other approaches – though little progress has been made.² In order to drive efficiency in the ethics review process via the use of central IRBs, the FDA might consider requiring Sponsors who are seeking to develop a new product under the Breakthrough Therapy designation to agree to use only research sites that will accept mutual recognition for central IRB review of multi-site trials or, at a minimum, commit to IRB review within a stipulated period of time (e.g., 30 days). Simply, if a therapy is important and promising enough that the Agency grants it priority and agrees to move quickly, all parties engaged in the project – sponsors, IRBs and investigators – should be similarly committed to efficient and timely processes.

Section V, G: Subject Participation in More Than One Clinical Investigation

In this section, the Agency states:

Some subjects may wish to participate simultaneously in more than one clinical trial or enroll in a single clinical investigation multiple times. FDA strongly discourages these practices as enrollment in more than one clinical investigation could increase risks to subjects, particularly because they may be exposed to more than one investigational product for which the safety profile may not be well understood. In addition, the subjects may find it difficult to understand all the risks and proposed benefits, much less meet the demands, of multiple protocols. Moreover, there may be potential drug or device interactions, and the simultaneous use of more than one investigational product may confound the results of the clinical investigations.

Sponsors generally include prohibitions related to the use of concomitant medications in the protocol or restrict (via exclusion criteria) inclusion of subjects who have participated in another clinical investigation within a specified period of time (for example, the washout period before a subject can enroll in a new clinical investigation). Implied in the prohibitions on concomitant medications is the idea that subjects should not participate in more than one clinical investigation.

Especially given that "Subjects receiving simultaneous investigational drugs" is identified as a deficiency code (13) in the Clinical Investigators Inspection List (CIIL) Database Codes³ – per 21 CFR 312.60 – ACRO believes the Agency should go further in exploring the issue of simultaneous participation. When subjects simultaneously participate in more than one clinical trial – and, are, thereby, possibly exposed to more than one investigational drug – this raises not only subject-safety concerns, but also data quality issues. Several companies in the United States claim to offer HIPAA-compliant research subject databases and registries that "solve" the problem of simultaneous participation for Phase 1 trials at least. But real concerns remain, including the dual challenges of comprehensiveness and inclusiveness

² 2006 – FDA Guidance for Industry - Using a Centralized IRB Review Process in Multicenter Clinical Trials
2009 - Call for Public Comment on Rulemaking to drive Central IRBs
2011 - Secretary's Advisory Committee on Human Research Protections (SACHRP) Letter to Sec. Kathleen Sebelius outlining recommendations
2012 Report from FDA, industry and academic-supported Clinical Trials Transformation Initiative (CTTI)

³ [Clinical Investigator Inspection List \(CIIL\) Database Codes](#)

of the registries, on the one hand, and protection of patient privacy and confidentiality, on the other. In order to drive toward a solution to the problem of subjects participating in more than one clinical trial, the Agency might consider, first, funding research to assess the frequency and seriousness of the problem. The FDA might also convene stakeholders – investigators, IRBs, sponsors and CROs – for a workshop to thoroughly discuss potential solutions.

In conclusion, ACRO appreciates this opportunity to comment on FDA’s Draft Guidance, and we look forward to further dialogue with the FDA about the important issues raised in this Request for Comments.

Respectfully submitted,

A handwritten signature in blue ink that reads "Karen A. Noonan". The signature is written in a cursive, flowing style.

Karen A. Noonan
Vice President, Global Regulatory Policy