

ACRO

ASSOCIATION OF CLINICAL
RESEARCH ORGANIZATIONS

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

[Docket No. 2004-N-0181]

Critical Path Initiative

Dear Sirs:

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 medical products. The Association of Clinical Research Organizations (ACRO) was formed in 2002 to represent this key segment of the clinical research enterprise to legislative and regulatory bodies. ACRO member companies employ more than 40,000 people worldwide, conduct research in 60 countries, and represent a multi-billion dollar industry.

ACRO member companies provide a wide range of research and development services to help pharmaceutical, biotechnology and medical device companies bring new drugs and new treatments to patients safely and quickly. In fact, research sponsors often transfer to a CRO some or all of the regulatory responsibilities stipulated by applicable FDA regulations (21 CFR), including Parts 11, 50, 54, 56, 312 and 314. CROs are tasked with strict vigilance of all stages of the clinical trial process to ensure compliance with laws, regulations, and industry standards, which are designed to protect human subjects, and to ensure the integrity of the scientific data on which medical product approval relies. The success of CROs depends upon high ethical and professional standards, and consistent compliance with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) guidelines.

The services of CROs are interwoven into the activities of all the participants involved in the clinical trial process, including sponsors, investigators, IRBs, monitors, DSMBs, regulators and patients. In many ways, our role is unique, as we function as associate, partner, intermediary, monitor, consultant and auditor, and we often endeavor to facilitate communication and collaboration across stakeholders. Thus, rather like the FDA, ACRO

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members have a cross-cutting view of the activities of many of the entities involved in medical product development, and we bring a broad perspective to the task of identifying opportunities for improvement along the pathway.

ACRO is pleased to provide input regarding activities that could reduce existing hurdles in medical product design and development, as described in the March 2004 report entitled *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. As companies whose primary tasks include increasing efficiencies, thereby reducing time and costs in the conduct of clinical research, while at the same time protecting patient safety and data integrity, CROs observe some of the ways in which regulation – and misinterpretation of or uncertainty about regulatory requirements – impede innovation, and we offer here five categories of ‘hurdles’ and ‘solutions’ for inclusion on a Critical Path Opportunities List:

1. Sub-optimal Communication between FDA and Stakeholders

ACRO member companies applaud the significant improvements in review processes and timelines that have been achieved since the passage of the Prescription Drug User Fee Act (PDUFA) and the FDA Modernization Act (FDAMA). We note, however, a similar and continuing need to streamline and speed the process for the development and promulgation of agency *guidances*, which provide useful and necessary direction to stakeholders, including sponsors, CROs, research institutions, investigators, IRBs, and others. Too often the existing process for the development of new guidances is halting, if not entirely static. And, notwithstanding the agency’s commitment to allowing broad discretion and flexibility in individual stakeholder application of any given guidance, which should be continued, in light of the agency’s access to process information across stakeholders, we believe there is potential for guidances relating to clinical practice to be derived more often from observed results and problems. Currently the FDA engages stakeholders in the guidance process in formal and slow ways, with the issuance of drafts and proposals and drafts and final guidance documents. ACRO suggests that a variety of ways to speed this process be considered, perhaps by way of having standing, cross-industry guidance advisory committees that meet on a regular basis, somewhat analogous to the Expert Working Groups used in the international conference on harmonisation (ICH) process. ACRO recognizes that dedicated resources are in short supply within the agency, and believes that many stakeholders would be willing to contribute appropriate resources to help support the agency in developing a more timely and specific guidance process.

Again, ACRO notes that there have been improvements in the provision of *scientific advice* by the agency to research sponsors. For instance, the use of special protocol assessment (SPA) and product development protocol (PPD) mechanisms has established clearly defined timeframes, along with levels of ‘commitment’ by the agency to agreements made in such areas as trial design, use of prior data, numbers of trials, etc. Because readily available and consistent scientific advice from the agency is invaluable to research companies, and perhaps especially to smaller and less experienced sponsor companies that often access the infrastructure and resources of CROs, ACRO would

encourage expanded use of SPA, PDP and similar mechanisms, and recommends greater oversight of the scientific advice process by senior FDA staff. We strongly support the idea that applicants should establish an ongoing dialogue with the agency early on, and throughout, the development process, which is something our members are often in a position to encourage, because as CROs our role is to advise sponsors on the best way to develop their products, and this includes helping to facilitate an effective working relationship with the FDA. We also acknowledge the FDA's limited resources for such meetings, and encourage the use of other forms of communication where appropriate, to limit the amount of agency resources needed for meetings, while permitting face-to-face meetings when those would be the most effective means of discussing the issue(s) at hand.

2. Standardization of Forms and Processes

As the agency is very much aware, there is enormous variability in the structure and content of the *forms and processes* utilized by the array of stakeholders involved in the clinical trial process. While some of this variability is an expected result of proprietary approaches to important topics, we believe much is unnecessary and has the effect of introducing inefficiencies and potential error. For instance, ACRO believes that parts of the *case report form*, such as patient demographics, past medical history, concurrent medicines, and the adverse events page could be standardized in reasonably short order, leading to less confusion among investigators and sites, and speeding monitoring, audit and inspection procedures. Of course, this would require serious dialogue between the agency and the relevant stakeholders to make the case for this change in approach and a commitment from the agency to accept data in a standardized format.

In regard to the *monitoring* of clinical trials, it would be useful for stakeholders to know what information is actually useful to the FDA, and a guidance or other statement from the agency to reinforce the intended focus of the monitoring process/visit on patient safety and data integrity would be very helpful. ACRO believes that it is possible to streamline the monitoring process and, again, to standardize the format and content of monitoring documents, such as trip reports. Similarly, a guidance or statement from the agency that would help to focus *data cleaning* activities on relevant safety and efficacy data would allow sponsors, CROs and others to capture genuinely relevant data, while reducing a meaningful barrier in the current pathway.

To address the standardization of such topics as case report forms and monitoring visit processes, ACRO recommends that the FDA request input from stakeholders regarding forms and processes, such as those mentioned above, that could be reasonably 'standardized' without undue burden or loss of proprietary interest, and then convene a stakeholder conference intended to produce documents and agreements within a set timeframe.

3. *Safety Reporting and Pharmacovigilance*

The safety of human participants in clinical research is a core issue for ACRO members, and the Association applauds the FDA's interest in modifying current safety reporting requirements to address the potential for the under-reporting of adverse drug reactions, and to provide additional data to the agency to better evaluate the relationship between specific drug and biological products and adverse events that may be associated with their use, as described in a proposed rule for "safety reporting requirements for human drug and biological products" published on March 14, 2003. Further, we support the implementation of safety reporting standards consistent with those recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

We believe that there is very little under-reporting of serious adverse events (SAEs) in clinical trials that are conducted under FDA regulations, and we are concerned that the definition of suspected adverse drug reaction (SADR) that has been proposed by the FDA will result in a significant increase in the number of safety reports submitted to IRBs and to the agency, with a consequent exacerbation of the noise-to-signal problems seen today. That is, the potential exists that IRBs could be inundated by written IND safety reports of serious SADRs that were unexpected, especially in large, multicenter, phase III trials. Since a SADR relationship to study drug, under the proposed definition, "cannot be ruled out", the vast majority of what are today called serious adverse events (SAEs) will be assessed as possibly related to study product. Under the proposed rule, the process of causality assessment will in most cases default to 'related' and thus generate the potential to increase dramatically the number of written IND safety reports.

What is needed, ACRO believes, are *new tools for signal detection* in the pre-approval environment, which can assure the agency of adequate safety oversight and improved decision making while, at the same time, not overburdening review boards. One approach to consider that would allow IRBs to focus on trends rather than isolated events would be to decrease the number of isolated IND safety reports from clinical trials by requiring sponsors of large studies (for example, of greater than 150 total patients) to submit to review boards regular (monthly, bimonthly, quarterly, other) blinded, tabular summaries of all serious SADRs, sorted using standard coding dictionaries. Under this approach the agency could still define certain individual events as requiring immediate IRB notification when they result in an IND safety report. For example, the agency could require that the same list of "medically significant" SADRs defined as "always expedited reports" in the post-marketing environment be reported to investigators and IRBs within the same timeframe as the report to the FDA. Another approach the agency could encourage is to expand the use of DSMBs or similar entities over more clinical trials, both to review safety issues and to assess efficacy (statistical power) earlier in the process.

ACRO recognizes that revisions to current safety reporting requirements and methods via new rulemaking would be a lengthy process, and one that should be coordinated with other federal agencies, including those that have endorsed the Common Rule. In the meantime, we suggest that the agency consider issuing a guidance to address certain particularly unwieldy aspects of current safety reporting, for instance by clarifying that every SAE report need not be accompanied by a written narrative.

4. IRBs, Investigators and Patients

While considerable improvements have been made since the 1998 OIG report entitled, “Institutional Review Boards: A Time for Reform”, it remains true that the current IRB ‘system’ has more work, more perceived regulatory responsibilities and burdens, and fewer resources than would be optimal. On one level, current procedures for both approval and oversight of clinical research depend heavily upon the IRB. On another level, while the IRB undertakes the determination of whether a research protocol is appropriately designed for the protection of participants and broadly meets a risk-benefit analysis, when a study is actually conducted it falls to sponsors and their CRO partners to provide specific individual investigator and patient-by-patient oversight: to assess the planned and actual recruitment of participants, the execution of informed consent, the collection and safeguarding of data, the reporting of adverse events and the use of data and safety monitoring boards (DSMBs), deviations from and changes to study protocols, and the like. In particular, the role of the study monitor – a research professional who has an ‘on the ground’ presence that is not within the scope of an IRB – is critical to the protection of clinical trial volunteers and to the integrity of research data.

IRBs have a critical function, but too often become bogged down in fulfilling multiple roles within an institution, such as serving as an institution’s privacy office, and tasks that have little to do with patient safety. In ACRO’s view there is a pressing need to *revise IRB regulations and clarify interpretations* of those regulations so that there are neither differing or ‘layered’ sets of IRB requirements for FDA-regulated versus federally-funded research nor varying levels of oversight depending upon the site where research is conducted. Further, ACRO recommends the exploration of a number of solutions for IRB time delays that would in no way compromise patient safety, such as significantly broadening the criteria for expedited review of protocol amendments. Finally, although there is widespread recognition that the current research environment is extraordinarily changed from what existed when IRB regulations were first promulgated, we believe that the FDA, along with other stakeholders, including other federal agencies, must devise mechanisms that will make central IRB review of multi-center clinical trials the rule and not the exception.

A number of the suggestions made to this point, such as the standardization of forms and processes, would serve to diminish some of the performance variability and levels of error observed across investigators. Because the steps of identifying, recruiting, training and retaining clinical investigators constitute a significant hurdle along the development pathway today, ACRO has been pleased by the emergence of *investigator training and certification programs* offered by several professional associations. We recognize the

value of improving investigator knowledge and understanding of regulatory and scientific requirements and stand ready to work collaboratively with sponsors, associations, research institutions and the agency on initiatives to increase the number of well-trained and committed clinical investigators.

As with investigators, difficulties with the identification, recruitment and retention of human research participants for clinical trials create significant time delays and cost increases in the product development pathway today. Certainly, there are multiple factors involved in this pathway hurdle, but we believe that *public understanding of and confidence in the research enterprise* is an issue and must be improved. Again, ACRO suggests that collaborative initiatives to explain clinical trials research and to present the enormous value of such research to the public at large should be undertaken by sponsors, research institutions, professional associations and the FDA.

5. *Re-engineering the Clinical Trial Process*

To this point ACRO has attempted to identify reasonably specific barriers in the existing product development pathway and to suggest initiatives to address those hurdles. But the spirit of the Critical Path Initiative is further reaching perhaps, calling for “*new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs.*”

Because many of the increases in costs and time delays occur within the development phase, between discovery and product launch, ACRO urges the FDA not only to consider but also to ‘experiment’ with new development tools, and new ways of getting to go/no go decisions faster, many of which the agency has discussed – but not implemented – in recent years. These include:

- greater encouragement for, and acceptance of, large single study designs;
- greater encouragement for, and agreement to, adaptive designs intended to identify true responders, speed characterization of product safety profile, etc.;
- development, validation, and increasing use of, surrogate endpoints;
- consideration of new safety thresholds in the assessment of certain drug characteristics that have proven particularly likely to cause safety problems;
- movement toward expanded use of electronic data capture and real-time review of safety data;
- and increased use of registry/risk management approaches during the development phase, when appropriate.

Beyond the development and use of these kinds of tools on a case-by-case basis, the FDA could *consider a fundamental redesign of the current clinical trial model*, for instance by allowing designs that would ‘collapse’ phase I and phase II to more quickly establish basic safety and efficacy, and then providing for a limited or ‘conditional’ approval of the drug or biologic, while requiring ongoing collection and submission of safety and efficacy data. That is, the agency could require more robust proof of concept trials and grant conditional marketing approval during what would now be phase III, which would

have as one effect the collection of a 'true' safety profile in a more timely fashion. In fact, the agency already has considerable experience with this kind of development pathway, via the use of programs that allow compassionate use, expanded access, accelerated approval and 'treatment' IND programs.

ACRO recognizes that any significant change to the current clinical trial model would require considerable deliberation and, ultimately, sign-on by stakeholders. We appreciate also a level of tension between genuine commitments for greater transparency by both sponsors and the FDA and the real need to protect confidential and proprietary information. Currently, however, the agency possesses enormous amounts of information relating to 'failed' development efforts, yet has neither the mandate nor the resources to review that data and to use it to develop and disseminate the very kinds of new evaluative tools that the Critical Path calls for. One option that would allow the agency to access outside resources and collaborate with a third party to initiate the development pathway research envisioned in "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" is a *cooperative research and development agreement (CRADA)*, and ACRO would be pleased to consider participating with the agency in such an agreement. Another option would be for the agency to create a standing Advisory Committee on Critical Pathway Tools, and to convene that group on a regular, (perhaps quarterly,) basis.

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As we know is true of research sponsors and other stakeholders, the Association of Clinical Research Organizations is genuinely excited by the potential of the Critical Path initiative, and pleased to suggest the issues outlined here for inclusion on the Critical Path Opportunities List. As we all look for ways to more effectively and rapidly provide new medicines and new treatments to patients, while at the same time assuring patient safety and maintaining the highest standards of quality and integrity in the product development process, ACRO believes it can be of assistance and looks forward to working actively with the FDA as it moves to gather information and initiate new activities to modernize and improve the product development pathway. We support a vision that has the potential to move the FDA from being a rules-based overseer to becoming a scientific standards-setting organization that collaborates with stakeholders to facilitate the creation of valid "new tools" that will speed the availability of safe and effective medical products.

On behalf of the Association of Clinical Research Organizations (ACRO), thank you for the opportunity to provide these comments.

Sincerely,



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Executive Director

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