15 August 2014

Office of Drugs Controller General
Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
Government of India
FDA Bhavan, ITO, Kotla Road
New Delhi -110002

RE: Proposal for Creation of an IT-Enabled System for Clinical Trials (issued 28 July 2014)

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations. Our member companies provide a wide range of drug development services, including the conduct of clinical trials. With more than 100,000 employees engaged in research activities in some 115 countries, ACRO member companies advance clinical outsourcing to improve the quality, safety and efficiency of biomedical research. In India, ACRO members employ more than 7,000 individuals and conduct approximately three-quarters of all industry-sponsored clinical trials.

However, we note that, over the past three years, the Indian business environment for clinical research has been characterized by growing regulatory uncertainty. And, as a result, India's participation in the global research enterprise has come to a virtual halt – to the detriment of the Indian population.

As an active stakeholder on Indian regulatory issues, ACRO has provided detailed comments on a variety of proposed regulations concerning the conduct of clinical research in India – including Serious Adverse Event (SAE) reporting; registration of CROs; compensation for trial-related injuries and deaths; and roles and responsibilities of Ethics Committees. These comments have been founded on the experience of our members around the world and our belief that a harmonized system of global regulation best ensures both the health and welfare of research participants and the quality and integrity of the data generated in the clinical trial.

ACRO welcomes and appreciates CDSCO's issuance of the above-referenced Proposal and the commendable objective of bringing transparency to the clinical trial process in India. Availability of robust, transparent, functional systems and processes is a necessity for establishing a thriving clinical research environment in the country. However, the Proposal raises a number of questions and concerns.

Public data elements and private data elements are not specified

As CDSCO undertakes this massive IT project, ACRO encourages you to provide general and specific assurances regarding the security of the system. In addition, public and private data elements must be clearly defined. It is currently unclear how much/what parts of the IT-enabled system will be publicly accessible. ACRO recommends that, for each section of the database, CDSCO should clarify who will have access to it and the security arrangements that will be put in place to prevent unauthorised access to non-public data elements (a security breach). In view of the potential for release of both (1) an individual's personal and private information and (2) sensitive commercially confidential information, we recommend that CDSCO should undertake a separate consultation exercise to determine the data elements that will be made public.

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The link – if any – between the IT-enabled system and the Clinical Trials Registry is not specified
It is unclear whether there will be any link between the proposed IT-enabled system and the current Clinical Trials Registry – India. Will CTRI continue as a separate entity or be absorbed into the new IT-enabled system?

Data access and management authorizations are not specified
ACRO recommends that CDSCO explain in detailed guidance – as well as regulation – the procedures for securing access to the system via documented, unique user names and unique passwords for each user. The levels of access and permitted activity should be clearly defined. The proposed IT-enabled system will require clear authorisations with regard to who can upload, edit, make changes and maintain the information. Stakeholders should have access to only those studies they are conducting.

Personal data capture is inconsistent with worldwide regulatory practice; the data retention policy is not specified
The proposal states that it is important that all information related to four major domains of a clinical trial in India are captured. These domains include detailed patient information/identification, details which are not captured by any other regulatory agency in the world. Moreover, it is a general principle of data protection laws globally that an individual's personal data should be used and retained only for as long as necessary for the identified purpose for which it is collected. In addition to clarifying the purpose for collecting such data, CDSCO should specify how long the information will be retained. Therefore, ACRO recommends that the IT-enabled system **not** capture the personally identifiable information of clinical trial subjects and, instead, utilize only key-coded or anonymized data.

Will the IT-enabled system comply with data protection and employment laws?
The proposal raises many concerns related to the protection of the private information of identified individuals (patients, investigational site staff and Sponsor/applicant staff) that will be entered into the IT-enabled system. CDSCO should explain how compliance with these requirements will be achieved under the data protection and employment laws in place in India. At a practical level, there are implications for consent to publication of private data (where these will be in the public domain) to be included in patient informed consent forms, Sponsor/applicant staff employment contracts and investigational site staff contracts, and CDSCO should provide guidance on how these issues should be managed lawfully. In particular, can an employer (Sponsor/applicant or investigational site/investigator) make such commitments on behalf of its staff or must each individual staff member consent individually? Has CDSCO considered the implications for clinical research in India should individuals refuse to give such consent and therefore be unable to participate in a clinical trial?

CDSCO should perform a benefit-risk assessment of the daily update requirement
The obligation to update information in the IT-enabled system on a daily basis will require significant resources on the part of, particularly, investigational site staff which will take such individuals away from their primary duty of providing healthcare to sick patients. We recommend CDSCO to perform a benefit-risk assessment of the collection of information to ensure that the resources required for collection are proportionate to the benefits of including the data within the IT-enabled system, and to eliminate requirements for updating of information that will not add value to the regulation of clinical research.

CDSCO should establish timelines for data updates
We recommend that CDSCO should establish clear, reasonable, and proportionate timelines within which information in the IT-enabled system should be updated following a change to information in the system or availability of new information.

CDSCO should create an ombudsman
In case of any dispute between stakeholders in relation to the IT-enabled system, we would encourage CDSCO to appoint an ombudsman responsible for investigating and reaching a decision on complaints related to use of the system.

Unique Identification Number (UIN) should be obtained by sponsor prior to data entry
The proposal states that once the information regarding a particular trial is put in the IT-enabled system, it would generate a Unique Identification Number (UIN) specific to the trial. It would be preferable for the sponsor to obtain the UIN first, prior to inputting of any data, so that the sponsor can communicate the UIN to all responsible parties (e.g., investigators, ethics committees) to ensure that, from first input, all data is linked to the UIN.

CDSCO should adopt electronic clinical trial applications that would automatically populate both the IT-enabled system and the Clinical Trials Registry – India
The proposal also states that the Sponsor/applicant, EC and Investigator will be required to upload Annexure A information before initiating or making the clinical trial application to CDSCO. As most of this information is included in the clinical trial application, ACRO recommends that CDSCO should move to a process of electronic submission of a clinical trial application form so that these data can be provided once only and the IT-enabled system populated directly from the clinical trial application. This will ensure accuracy of the information in the database relative to the clinical trial application and eliminate the resource requirement for both CDSCO and other stakeholders to reconcile information in the application and the database. Similarly, auto-population of information required in the Clinical Trials Registry – India from the electronic application form should also be facilitated to avoid duplication of resource requirements and potential for error/inaccuracy (if the CTRI is to remain as a separate database).

Annexure A, Section C requirement regarding protocol treatment is unclear
Requirement #3 which states: "In the protocol treatment is defined only by active substance?" is unclear.

Annexure A, Section H requirements are impractical and should be deleted
Some information requested in section H of Annexure A (e.g., whether any subject experts were included in ethics committee meetings, number of EC meetings conducted in respect of the trial, details of EC opinion) will not be available at the time of the initial application and therefore should not form part of Annexure A.

Annexure A, Section I requirements regarding pathology lab is unclear
ACRO recommends that the requirement to enter the "Name and address of Pathology lab for testing and whether GLP certified" should be moved from Annexure A, Section I ("Investigator") to Annexure A, Section F ("General Information on the Trial"). In addition, ACRO asks CDSCO to clarify and confirm that

the laboratory information requirement is for local lab facilities and is not applicable to central laboratories located outside of India.

How the IT-enabled system will manage a change of legal entity is not specified
The proposal requires stakeholders to upload Annexure C information after completion of the trial and before making the application for marketing authorization. As the Sponsor/applicant for the clinical trial may not be the same legal entity that applies for marketing authorization (and, indeed, the Sponsor/applicant may change during the course of a clinical trial), CDSCO should explain how a change of legal entity will be managed in the IT-enabled system.

The terms "Sponsor," "Applicant," and "Legal Representative" need to be defined (including responsibilities)
The proposal refers variously to Sponsor/applicant and Legal Representative of the Sponsor in India (in case of foreign sponsor). The distinction between these terms and the respective responsibilities of the Sponsor, the applicant and the Legal Representative should be clearly defined.

Requirement for Monitor name and contact information is impractical and should be eliminated
Section C of Annexure B requires the name and contact details of the monitor of the trial. The value of this information to the regulation of clinical trials is unclear and the requirement should be eliminated. It is unclear whether the proposed information will relate to the clinical research associate or the medical monitor or both. Further, this requirement does not reflect the modern reality of clinical trials where there is increased use of remote monitoring and centralized monitoring techniques which, in certain types of trials, may negate the need for a local monitor.

CDSCO should clarify inspection provisions
Sections B and C of Annexure C relate to inspection of trial sites and the IMP manufacturer/importer. The scope of information required in these sections is not clear – will information be required for inspections related to the clinical trial conducted in India by any regulatory agency or only for inspections conducted by CDSCO? If the latter, we recommend that that CDSCO should input the relevant information to the IT-enabled system in order to ensure consistency.

Annexure B, Section C monitor requirements should be revised
The responsibilities for monitoring are assumed either by the sponsor or the CRO appointed by the sponsor. These details are stated in the letter of delegation of authority issued by the sponsor. The individual monitor is a representative of the sponsor/CRO. Therefore, ACRO recommends rewording this requirement to request the entity name, rather than an individual name: "Name of the **entity** responsible for monitoring, its address and phone number."

Annexure B, Section D is repetitive and should be deleted
Ethics Committee details are captured in Annexure A. Therefore, ACRO recommends deleting this requirement in Annexure B.

Annexure B, Section E "substantial amendment" is unclear
ACRO recommends defining and clarifying the types of changes that would be considered "substantial amendments."

Annexure B, Section F requirements for trial subject details are impractical
As already state above regarding personally identifiable information, ACRO recommends the deletion of the requirement for name, address, and annual income in this section. In addition, because not all randomized subjects complete the study, the requirement to capture randomized subjects does not serve any specific purpose and should be deleted. Finally, ACRO recommends revising the expectation to update the number of randomized subjects in the system to a reasonable frequency – such as once a month or once in three months (rather than daily).

Annexure B, Section G SAE information requirements are premature
To avoid submission of premature information pending decisions, we recommend that details of individual SAEs (nature, cause in the event of death, compensation) in section G of Annexure B should not be submitted until after the final determination/recommendation of the DCGI is available.

Thank you for the opportunity to provide comments on this important Proposal. We look forward to working with you to achieve a regulatory framework that both ensures that the best interest of the patient is protected and provides an environment that is conducive to the development and evaluation of new medicines in India.

Respectfully,

Douglas J. Peddicord, Ph.D.
Executive Director