



AIIMS/MRCT/AHERF

January 21-22, 2014

Implementation Roundtable: Follow Up on Regulatory Changes Relating to Clinical Trials in India

EXECUTIVE SUMMARY

Introduction

These recommendations embody the consensus of different stakeholders, including leading academicians, investigators, industry representatives and government officials who met on January 20 and 21, 2014 to discuss the proposals of Prof. Ranjit Roy Chaudhury's Committee. This document also suggests additional issues that the Ministry of Health and Family Welfare, Government of India, may wish to reconsider when implementing the reforms involving clinical research regulations in India.

The roundtable met to discuss (1) implementation of the Ministry of Health and Family Welfare's decision to require accreditation of ethics committees, investigators, and clinical trial sites, (2) the benefits, risks and costs of the order requiring audiovisual recording of the informed consent process of all clinical trial subjects in India, (3) the utility of data from foreign clinical trials for India regulatory approvals, (4) issues related to the compensation mandate including the complexity of causality assessment, (5) the draft proposal regarding criminal and civil penalties for non-compliance, and (6) any other issue related to the recent clinical trial regulation reforms. The two days of vigorous debate and conversation ended with the consensus and considerations provided below. The executive summary of the roundtable is presented here.

(1) Accreditation of sites and ethics committees; certification of investigators

The **National Accreditation Council** should be constituted and charged as soon as possible. The Council, government-funded and comprised of 3-5 independent content experts, will function autonomously; determine a framework and timeline for accreditation of sites, investigators and ethics committees; establish standards for accreditation and certification; and assure that review of sites, investigators and ethics committees is of sufficient quality to ensure that clinical research in India is of the highest quality. The Council will determine the qualifications of organizations that seek to accredit and be authorized to delegate accreditation responsibilities and authority to such qualified bodies. The Council will review and certify all training programs and any institutions that offer clinical research training programs for quality. The Council may have advisory committees to assist it in its work.

The roundtable noted that it would take considerable time for all organizations to be accredited and for investigators to be certified but, eventually, universal accreditation and certification is the goal. No organization or investigator should be exempted from the process or from the Council's directives. That said, the Council should be charged to develop a process by which ongoing trials may continue and new trials may commence while accreditation and certification programs are being developed and implemented. This process should consider a risk-based approach to ensure the health and safety of research participants.



Investigator Certification. One or more organizations will assume responsibility for certification of investigators; “investigators” will include principal investigators, site investigators and co-investigators. Standards for certification will be set, self-assessment tools created, and training and education programs developed. Under current regulation, no investigator may assume responsibility for more than three trials; the roundtable believes that this (and any) numerical cap should be eliminated as the nature and demands of clinical trials differ.¹ While only investigators will be required to be *certified*, all individuals involved in human subjects research will be mandated to demonstrate competence in good clinical practices (GCP) and, to fulfill this objective, quality GCP training programs will be developed and offered throughout India.

Site Accreditation. One or more organizations will assume responsibility for accreditation of sites. The accrediting bodies will develop published standards and self-assessment tools, perform rigorous review of policies and procedures, and develop published review criteria. Accreditation will be based on one or more site visit inspections and demonstration that policies are indeed embodied in performance. It was felt that institutions, and not individual divisions or departments, were the right unit of accreditation, and that the institution should develop procedures to determine qualification of its more discreet units, including community affiliates. After a defined, limited period of phase-in of the requirement for accreditation, phase 1, 2 and 3 trials would only be performed in accredited sites. The National Quality Council has offered to be of assistance in this effort; potentially a division within the National Quality Council could be constituted for accreditation of sites. However, other modalities of accreditation should be considered. A plan for new site entrants to clinical site accreditation should be developed.

Ethics Committee Accreditation. One or more organizations will assume responsibility for accreditation of ethics committees. The accrediting bodies will develop published standards and self-assessment tools, develop review criteria that will be publically available, and perform site visit inspections. It was clear from the discussion that the ethics committees did not uniformly have the resources to perform some of the assigned tasks. ECs should have sufficient authority and resources (time, space, human and financial) to perform their work. The ECs should develop quality assessment programs to monitor the trials for which they are responsible, and the ECs should themselves be monitored. FERCI and the Association of Accreditation of Human Research Protection Programs (AAHRPP) have offered to be of assistance in this effort; multiple pathways to accreditation may be considered.

Education: A comprehensive educational platform for improving the performance, roles and responsibilities, and expectations for the ethical and robust execution of clinical trials is essential. Education of EC members, investigators, and all individuals involved in the clinical research enterprise is an immediate need. In addition, educational programs for potential participants in these activities should commence. The scope of educational responsibility should not be limited as, for instance, non-technical members form an important component of ECs. These educational

¹ For example, some trials are still ongoing but in data analysis only, some are actively enrolling, some are dedicated to addressing the needs of patients with rare diseases (in which very few patients will enroll). At a minimum, there should be a process for consideration of an exception to any numerical cap.



programs should themselves be evaluated periodically. Capacity building is essential. Further, exposure to ethics and bioethics (vide infra) should begin in secondary school and to the elements of clinical research (randomization, blinding, statistics, etc.) in medical school. There should be separation between the educational offerings and the ultimate process for accreditation.

(2) Informed Consent Process and the Role of Videotaping.

The Government has ruled that videotaping of the consent process should be performed for all consents, principally as a means to document the robustness of the process. The roundtable felt strongly that the advisability of this rule should be reexamined and the rule modified. The roundtable agreed with the expert committee to limit videotaping to special situations for reasons of privacy, confidentiality and practicality. Alternative methodologies to demonstrate participant understanding and consent should be developed (e.g. report-back; independent witness). Alternatives to videotaping should be explored and studies initiated to examine different methods to ensure that consent is understood; these alternatives should not compromise privacy and should be respectful of cultural milieu. Videotaping should be reserved for vulnerable populations and special situations. Patient autonomy directs that participants should have the right to decline videotaping and nevertheless consent to participate in the trial. Further, to maintain participant privacy, sponsors should not have access to any video recording unless there are reasonable allegations of concern such as coerced consent. The responsibility to ensure that the audiovisual recording of the consent discussion occurs -- and is appropriately preserved -- should rest with the investigator(s). Detailed guidance should be provided on privacy and the technical aspects of storage and archival processes.

(3) Utility of data of foreign clinical trials for use in India.

The roundtable questioned whether there was a scientific basis to believe that ethnic differences may affect study outcomes or safety and whether bridging studies were necessary. Bridging studies necessarily incur a two to five -year study before regulatory approval, thus delaying the introduction of potentially important new drugs to India. Is the inherent “drug lag” introduced by bridging studies or 4-6 year monitoring detrimental to the Indian patient population? Is India one or multiple ethnicities? And are these differences significant compared with the post-market utilization in the real world? If so, why are certain classes of drugs exempted by rule? The Ministry should create a committee to further explore a process in which treatment outcomes across foreign regions are assessed, with bridging or other studies required only if pharmacological and/or efficacy differences are detected. This issue requires detailed discussion.

(4) Compensation and Causality Assessment.

India is poised to be a global leader in mandating compensation for clinical trial injury and death, and the roundtable appreciated the complexity of the undertaking. To date, only a formula for clinical trial-related death has been offered; guidance on *injury* compensation is yet to be provided. Injury presents the larger and more complex issue and much of the discussion at the roundtable centered on these issues. Several recommendations were made:



- a. A **national fund** should be established to provide a corpus for compensation for investigator-driven research and for research in which an academic institution or non-profit organization is the sponsor of the research. Compensation for injury should be provided regardless of the sponsor. The sponsors able to avail of this fund should be defined. For example, would an NIH-funded trial at a public or private academic institution be eligible to rely on monies from this fund for compensation? The fund could be used to help purchase insurance or to pay compensation directly; economic analysis will need to be performed. A process to review and approve the research to be covered by such a fund should be developed, to ensure that the research is meritorious and scientifically robust. The mandate may be given to the EC to serve this role. Notwithstanding a role for the EC, government oversight will be required to monitor the fund.
- b. Informed consent documents should clearly describe known potential side effects and potential anticipated and unanticipated adverse events. The availability of compensation should be contained in the informed consent document and discussed with prospective research participants.
- c. The informed consent document should convey that “adequate compensation” will be provided. The *specific* amount of compensation offered for injury or death should not be communicated widely. This recommendation for more general language in consent forms will allow flexibility and accommodate potential future changes in the compensation formula or other specifics of compensation.
- d. Ethics committees should demonstrate their capability to adjudicate causality; empanelling a subcommittee to determine causality and compensation to provide expertise and advise. Representation on any compensation committee should be diverse, including women and underserved populations. Adjudicators of all compensation issues must report financial conflicts of interests. Any conflicting financial interest should be disclosed and reviewed, and individuals with significant financial conflicts of interests should not adjudicate events that are in any way related to their financial interests.
- e. The roundtable was concerned that the EC, a body constituted to assess risk/benefit and the ethical conduct of research, was not the appropriate body to review causality and compensation. Convening a separate institutional committee or subcommittee to review all adverse events, causality and compensation should be considered. In this regard, the role of a data safety monitoring board should be considered. At a minimum, tracking the performance of the ECs, the reproducibility and variability in determinations, will be important.
- f. Capacity building and training, which are necessary due to the complexity of causality assessment, should be commenced immediately. Anyone involved in causality assessment and compensation, including EC members or members of an EC subcommittee (if one exists) should have mandatory training. Comprehensive educational efforts should be shared across the nation.
- g. Predictability of liability is important for the clinical trial enterprise. To limit liability for all sponsors and allow for affordable insurance premiums, the Ministry should cap the amount of compensation for injury and death at an amount less than the current amount of 73 lacks. That cap should be adjusted for cost of living annually, and adjusted at some periodicity, e.g. every 3-5 years.
- h. The roundtable did not review in detail the compensation formula, but encouraged the differentiation of known side effects from study-related injury, and the differentiation of anticipated versus unanticipated adverse events in compensation amounts.
- i. The roundtable favored further discussion and consensus to propose modification of the compensation formula such that it includes the weight of probability of a side effect (based on 4 or 5 categories of, unlikely, possible, probably, likely, and definite) factors into the

amount of compensation. Currently a “yes/no” binary determination, while simple, creates too much pressure on determination of causality that is, itself, probabilistic.

- j. The roundtable favored consideration of modifying the compensation formula such that the potential benefit of the therapy is considered. The nature of compensation should take into consideration, for example, whether a participant is offered a potentially life saving therapy or a normal volunteer exposed to a first-in-man drug.
- k. In order to preserve the integrity of ongoing and blinded studies, no clinical trial should be un-blinded for determination of causality. Mechanisms to determine causality without un-blinding should be developed. The role of the data safety monitoring board (DSMB) should be considered.
- l. The roundtable recommends that post-market surveillance and post-trial access to study drug or other test agent should be exempted from current compensation proposals.
- m. There should be consideration of exempting participants who have been inappropriately enrolled in trials (i.e. when a participant is entered into a trial but does not meet the predetermined eligibility/ineligibility criteria) and in the event of subject non-compliance.

(5) Draft proposal regarding criminal and civil penalties for non-compliance.

While the roundtable agreed that investigators, research staff and sponsors are responsible for their actions, criminal penalties with minimum sentences are disproportionately severe and will deter sponsors and investigators from funding or conducting clinical trials. Criminal prosecution should be reserved only for instances in which the government can demonstrate willful misconduct, gross negligence, and/or intentionality. To address unwarranted fears of criminal prosecution, the Ministry must stress that prosecutors will pursue criminal charges only when the government has found significant evidence of willful misconduct, gross negligence, and intentionality. Civil penalties for noncompliance, with financial fines sufficiently large to act as a deterrent, should be reserved for continuing or serious non-compliance. Other penalties should be considered: restriction of professional activities, debarment, and/or professional sanctions. If ignorance or simple error is at fault, education should be offered.

Other Recommendations

(6) Detailed definitions.

Clear definitions of a new drug, clinical trial, sponsor, academic versus non-academic trials, etc should be provided.

(7) Bioethics education.

India does not currently have formal curricula devoted to bioethics education. We recommend a focus on bioethics education: in secondary school and medical school, and the development of a graduate program in bioethics. Bioethics entails the examination of ethical issues in health care, health science and policy, and research involving human subjects. It is an ever-advancing field as new technologies and the application thereof are developed, and it is important that the Indian community is engaged in the public debate, given cultural sensitivities and the particulars of civil society. Professional pathways for trained bioethicists should be developed.



(8) Public Education and Engagement Campaign.

Civil society and the public should be actively engaged in the clinical trial enterprise. A campaign to educate and empower the public on the purpose of, and potential benefits and risks of, clinical trials should commence, as the value of new medicines and the benefit to public health cannot be overestimated. The campaign should be led by highly-regarded academic institutions and/or not-for-profit disease-specific organizations. Such a campaign should include voices of participants, the oversight to ensure the ethical conduct of research, and the protections in place to ensure, to the extent possible, the safety and wellbeing of human subject participants. Appropriate mechanisms to fund such an initiative without industry control of the education should be considered.

(9) Analytics, Feedback, Evaluation and Quality Improvement.

The redesign and accreditation of the clinical trial enterprise in India offers a unique opportunity to collect national data on the enterprise, develop a data analytic framework, and develop metrics that will inform the future. Such a framework should be developed and embedded in each accreditation and certification platform, and be centralized nationally for analysis and for purposes of internal comparative evaluation. Such data will then become the basis for quality assessments and for identifying areas for study, education, and continuous quality improvement. A flexible and nimble approach to data-driven redesign will ensure that India sets the global standard for quality, safety, and patient protections in the clinical trial enterprise.



Day 1 – Inaugural Conference Committee

From left to right: Mira Shiva (Initiative for Health Equity and Society), Rebecca Li (MRCT), YK Gupta (AIIMS), Keshave Diraju, (Secretary, Ministry of Health and Family Welfare), Barbara Bierer (MRCT/Harvard Medical School), MC Misra, (AIIMS), Ranjit Roy Chaudhury (Apollo), Sita Naik (Apollo), P. K. Julka (AIIMS)



Day 2 – Final Session

From left to right: Barbara Bierer (MRCT/HMS); GN Singh (Drug Controller General of India), YK Gupta (AIIMS), Ranjit Roy Chaudhury (Apollo), Shri RK Jain (Additional Secretary, Ministry of Health and Family Welfare), Uma Tekur (Maulana Azad Medical College)